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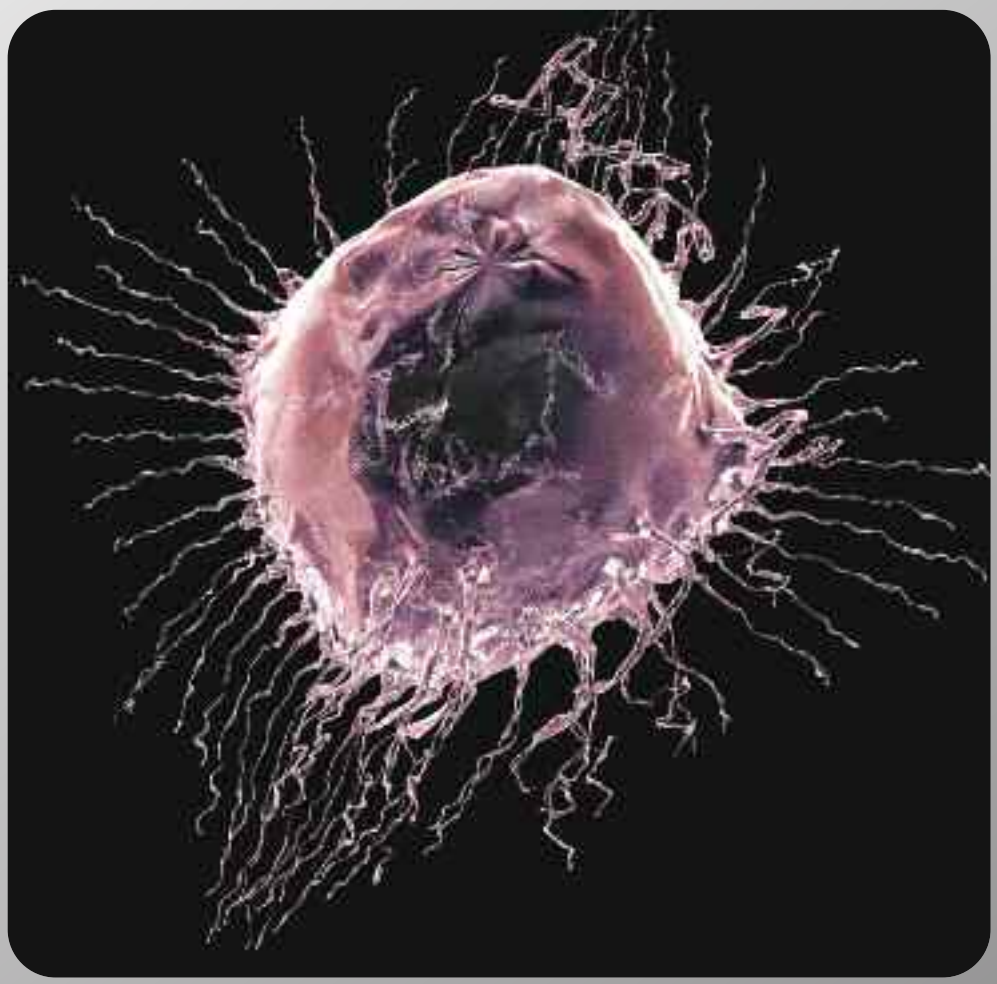

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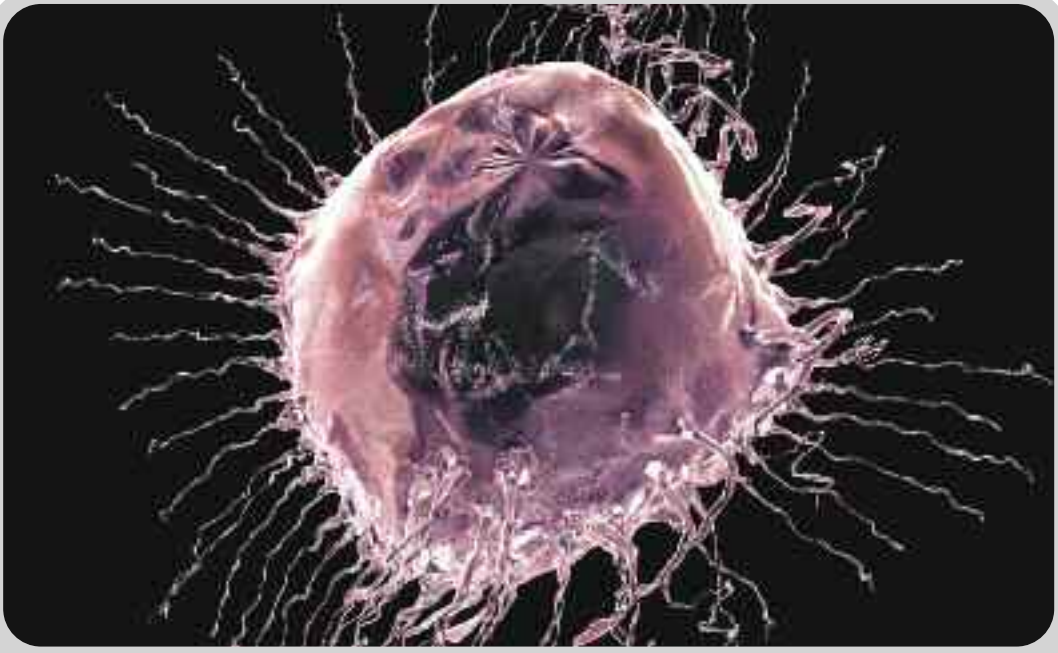

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Where there's a will there's a way

Editorial

Vassilios Barbounis

The 3rd issue is now published; five issues in total, if you also take into consideration the two special issues. I would like to thank you all for your contribution and your comments.

The journal addresses all scientists involved in oncology. It gladly receives articles from all parties interested to publish in FCO and those articles which satisfy the standards set by the editorial board are published without any discrimination as long as they respect the values and principles of scientific research, meet the goals of the journal and are presented according to the set guidelines.

No discrimination is made upon sex, age, academic position or geographical origin. On the contrary, we encourage people to submit their work. The editorial team puts a lot of effort and resources to deliver a publication at fine quality. We are aware that we have a long way to go until the goals of the journal are met but we are open to constructive criticism and ready to correct our faults. However, our efforts are not sufficient if we do not get the genuine support of those working in oncology. We need your work to make it.

Some colleagues have expressed difficulty to accept comments or benign criticism of their work through a peer-review procedure. However, such procedure is internationally recognized as the unique approach to secure high quality publications in any scientific, high level journal. Naturally, ours makes no exception. Likewise, occasionally, reviewers may get carried away and become improperly strict. Please rest assured that it is within the objectives of the editors to make sure this phenomenon is extinct.

As you may see in this issue, the number of articles has increased and the ratio is in favor of research articles versus review articles. A new column is also inaugurated, that of the readers, and I take this opportunity to invite you to contribute with your comments and remarks in the form of a letter to the editor.

Why peer review is needed

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Although practicing medicine may be partly an art, medical information ought to be concrete, logical and unquestionable. The medical profession perhaps includes a certain amount of empiricism but it should be distinguished from medical knowledge, which is solidly based on science. And science is relentlessly dependent on reason, proof, measurements and reliability. Knowledge that has the above characteristics, that is of being unequivocal, should not be confused with hypothesis and theorizing, which are useful in the methodology of developing knowledge -but not knowledge *per se*.

In addition, novel medical information ought to be relevant and interconnected with the already existing knowledge. It may fill gaps or open new territories in the vast area of the domain that can be approached by science. The methodology of extracting truth from observation, often based on statistics, should be crisp. Conventions should be clearly acknowledged; weaknesses of any medical observation should be clearly stated. In other words, the development of new knowledge must fulfill validity criteria; it must be humble and unassuming; it must be careful and not arrogant.

In the ideal city of Plato called Utopia, since it was ruled and controlled by wise men, there would be no need for peer review of scientific observations. All scientists would be presumed wise, perfect, impeccable, honest and thorough. Their observations would be robust and well-connected to the existing knowledge. However, in our actual world, where no gold standard exists, where opinions, attitudes and stances change as time goes by, nobody can guarantee such a thing as a wise oncologist -which is why we have a democracy rather than oligarchy. In cases of human relativity, the wise thing to do is not to rely on one but on many. We see this in everyday life. Courts consist of 3 or 5 members; there are always committees for important decisions; there are even medical boards or tumor boards for important health decisions. This is not because each person participating is incapable of deciding, but in human societies it is collectivity that establishes the accepted standard.

A particular medical manuscript aspiring to be published, in other words to be widely available and perhaps influence other physicians in the way they practice medicine, should either be written by the wise scientist of Utopia, or should have been previously screened, criticized and amended by a number of peers. This process may eventually improve the manuscript, may validate the research and render it useful and relevant. Each reviewer may offer his own perspective on the findings. Often, writers' enthusiasm may blind them to methodological weaknesses of the experimental part, or the impact may be overstated. Other omissions may be pointed out so that, if addressed, the manuscript will be more potent and convincing. Important or practical medical information may be asked for by the reviewers and thus increase the publication's practical value.

Naturally, the reviewers' job is a very responsible one. The goal is to help improve the submitted manuscript and bring it up to its full value. In other words, reviewers are assistants to writers and should not be thought of as nasty and strict castigators. They should approach the manuscript with the will to assist rather than demonstrate their potential superiority. If some of the comments made by the reviewers are thought as excessive, they could be addressed in a gentle response.

In conclusion, peer review is necessary for assuring a satisfactory level of relevance of the submitted research, for improving the manuscript to its full capacity. It has to be a non-offending, non-personal collaborative effort to enhance the quality of the paper; provide validity; and improve its possible deficiencies. In addition, we should all have the fear of arbitrariness, which is best served by having colleagues review our new proposed statements. Being a reviewer is a serious work, a sacrifice of time and effort on behalf of the reviewer for the sake of medical knowledge and as such it should deserve the utmost respect by the writers. Peer review is the essence of democracy, where we can all judge and be judged, thus avoiding fixed doctrines, and inflexibilities that tie us to the past, while everything is rapidly evolving around us. Nobody should be asking for immunity from criticism. Peers help us keep in track with the present and the needs thereof. And peers are whom we should address our speech to, anyway.

Predictive and prognostic value of the Glasgow Prognostic Score (GPS) in Greek patients with metastatic lung cancer

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ABSTRACT

Background: Lung cancer is the most common cause of cancer death. Most patients present with advanced disease and prognosis is generally poor. A cumulative prognostic score based on C-reactive protein and albumin, termed the Glasgow Prognostic Score (GPS), indicates the presence of systemic inflammatory response. GPS has been associated with cancer cachexia and has been proposed as a prognostic tool. The aim of this study was to assess the value of baseline GPS in Greek patients with metastatic lung cancer.

Patients & Methods: Patients referred to the Dept. of Medical Oncology from February 2006 to March 2008 for consideration of first-line systemic treatment were eligible. Demographics and disease-related characteristics were recorded. GPS was calculated before the onset of therapy. Response to first-line therapy and survival data were collected.

Results: Totally, 160 patients (142 males) were accrued. Most of them (78%) belonged to the good prognosis category. GPS was correlated with baseline BMI (p=0.012), history of weight loss (p=0.048), performance status (PS) (p=0.02) and the number of metastatic sites (p=0.004). For the 136 (85%) patients who received first-line antineoplastic therapy, GPS was correlated to both response rate (p=0.01) and time to progression (p<0.001). GPS was also correlated to overall survival in the total cohort (p<0.001) and in the subgroup of actively treated patients (p=0.004). In multivariate analysis, weight loss (p=0.03) and GPS (p<0.01) were independent predictive factors while the independent prognostic factors were PS (<0.01), weight loss (p<0.01) and GPS.

Conclusions: We confirm the prognostic and predictive value of GPS in Greek patients with metastatic lung cancer. We have also shown that GPS is related to other baseline characteristics indicating adverse outcomes.

Key words: lung cancer; prognostication; Glasgow Prognostic Score; inflammation; cachexia.

INTRODUCTION

Cancer-related cachexia has been defined as a process that frequently accompanies neoplastic diseases and is related to muscle wasting with or without reduction of fat mass (1). In practice, although loss of adipose tissue accounts for the greatest part of the weight loss, it is the muscle wasting that is considered to be mainly responsible for the morbidity and mortality observed in these patients (2, 3).

Evidence suggests that the presence of systemic inflammatory response is associated with increased weight loss, elevated resting energy expenditure, loss of lean tissue and functional decline, while the use of anti-inflammatory agents may reverse part of these clinical features (4, 5). C-reactive protein (CRP) is considered an essential marker of systemic inflammation and has been related to most of the aforementioned signs of nutritional depletion as well as overall survival (6-8).

Albumin represents a negative acute phase protein and its level decreases as CRP rises (4). In addition, lean tissue depletion is related to hypoalbuminemia (4). Low albumin levels have been also related to weight loss, increased morbidity and adverse outcomes in patients with malignant diseases (9). Specifically, in patients with non-small-cell lung cancer

(NSCLC), low albumin levels have been constantly related to poor survival (10-11).

For this particular primary, the prognostic value of the combination of an elevated CRP concentration (>10 mg/l) and hypoalbuminemia (<35 g/l) has been shown to be superior to the clinical standard combination of stage and performance status (12). Various reports in the literature support that this combination, termed the Glasgow Prognostic Score (GPS), is independent of tumor stage and conventional scoring systems; superior to performance status; and independent of treatment modalities for different primary sites (13-25).

In the present study we examined the predictive and prognostic value of baseline GPS in Greek patients with metastatic lung cancer.

PATIENTS & METHODS

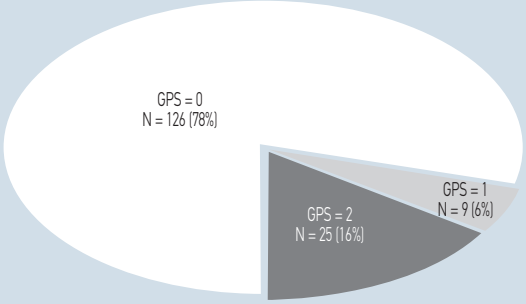
Eligibility

Patients, older than 18 years old, with histologically or cytologically diagnosed metastatic lung cancer, referred to the Department of Medical Oncology in the University Hospital of Heraklion for initiation of systemic antineoplastic therapy from February 2006 to March 2008, were eligible. Enrolled patients had to have measurable non-irradiated disease according to the RECIST criteria (26). Patients with a history of a second primary cancer, with the exception of non-melanoma skin tumor, were excluded. Patients with chronic diseases (e.g. chronic renal failure), that could significantly interfere with the measured laboratory parameters were also excluded. All patients provided written informed consent before study entry. The study was approved by the Ethics and Scientific Committees of our Institution.

Patient demographics and baseline characteristics

Basic demographics [gender, age, body mass index (BMI), weight loss history (cut-off 5% during the three preceding months) and smoking status], detailed medical history and medications, as well as patient baseline characteristics [Eastern Cooperative Oncology Group Performance Status (PS), histological type (non-small-cell lung cancer / small-cell lung cancer), number and location of metastases] were recorded. Baseline CRP and albumin levels were measured before the onset of first line antineoplastic therapy with standard methods.

Figure 1.
Distribution of patients in each GPS group



GPS assessment

According to the GPS, patients were categorized in the following 3 prognostic groups: Patients with CRP ≤10 mg/l were considered of good prognosis irrespectively of albumin value (group A), while patients with CRP >10 and albumin ≥35 g/l were of intermediate prognosis (group B) and patients with CRP >10 but albumin <35 g/l comprised the group of poor prognosis (group C) (4).

Follow-up

The subsequent systemic treatment was recorded. Depending on the efficacy of first-line therapy, patients were categorized as responders (complete/partial response) according to the RECIST criteria (26). Time to tumor progression (TTP) was defined as the interval from treatment initiation to first evidence (clinical, and/or radiologic) of disease progression or death from any cause. Overall survival (OS) was defined as the interval from diagnosis to death from any cause.

Study endpoints

Our objective was to evaluate the predictive and prognostic value of GPS in patients with metastatic lung cancer.

Statistical analysis

Data were analyzed using standard statistical methods (chi-square test, One-way ANOVA test). For survival analysis, the Kaplan-Meier method was used in order to compare the survival curves of each categorical variable. Statistical significance was determined by using two-tailed P values and was reported at $P<0.05$ level. Cox proportional hazards model was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for univariate or multivariate analysis. Statistical analysis was carried out using SPSS (SPSS for Windows, version 15.0, SPSS, Chicago, IL).

RESULTS

A total of 160 patients (142 males) [mean age (± standard deviation) 64.6 (±10.4)] was recorded. The distribution of patients in each GPS group is illustrated in Figure 1. Baseline patient and disease characteristics for each GPS group and comparisons between groups are depicted in Table 1. Moreover, GPS was correlated with both baseline BMI and weight loss history (p=0.012 and p=0.048, respectively).

One hundred thirty-six patients (85%) received some form of first-line systemic treatment; 38.4% platinum-based doublets,

Table 1.

Baseline characteristics for each GPS group and comparisons between groups

Parameter		GPS group – N (%)			p value
		A [98 (61.3)]	**B** [36 (22.5)]	**C** [26 (16.2)]	
Age [mean (±SD)]		63.5 (±10.2)	65.5 (±11.3)	67.2 (±11.2)	NS
Smoking status	Current smokers Former/Non smokers	78 (79.6) 20 (20.4)	26 (72.2) 10 (27.8)	20 (76.9) 6 (23.1)	NS
Histology	NSCLC SCLC	66 (67.3) 32 (32.7)	26 (72.2) 10 (27.8)	22 (84.6) 4 (15.4)	NS
PS	0-1 ≥2	68 (69.4) 30 (30.6)	17 (47.2) 19 (52.8)	10 (38.5) 16 (61.5)	0.02
No. of metastatic sites	<2 ≥2	53 (54.1) 45 (45.9)	15 (41.7) 21 (58.3)	8 (30.8) 26 (69.2)	0.004

39.2% non-platinum-based combinations and 22.4% monotherapy. The percentages of patients exposed to therapy were 96.7% for group 0; 72.7% for group 1; and 64.0% for group 2, and this difference was statistically significant (p<0.01). The percentage of patients who discontinued first-line therapy due to toxicity reasons was 2.4%, 4.3% and 23.1% for groups 0, 1 and 2, respectively (p=0.019). GPS was correlated with both overall response rate (ORR) (p=0.01) and TTP (p<0.001). ORR and median TTP were 44.8%, 20% and 3.8% and 4.7, 3.3 and 1.4 months for patients with GPS 0, 1 and 2, respectively. The hazard of tumor progression was 1.2 times higher in patients with a GPS score of 1 and 4.2 times higher in patients with a score of 2, as compared to 0 score. Kaplan-Mayer curves for TTP according to GPS are shown in Figure 2.

Furthermore, GPS was significantly related to OS (p<0.001). Median survival for GPS groups 0, 1 and 2 was 8.6, 3.8 and 1.6 months, respectively. The hazard of death was 1.8 times higher in patients with a GPS score of 1 and 4.2 times higher in patients with a score of 2 as compared to 0 score. Kaplan-Mayer curves for OS according to GPS are illustrated in Figure 3. For the subgroup of patients that received first-line therapy, the Kruskal-Wallis test revealed that overall survival was also significantly different between GPS groups (p=0.004).

In univariate analysis, age (p=0.04), weight loss (p=0.01), PS (p<0.01) and GPS were significantly related with TTP. Weight loss (p=0.03) and GPS (p<0.01) retained their importance in multivariate analysis. In terms of OS, weight loss (p<0.01), PS (p<0.01) and GPS (p<0.01) emerge as significant prognostic

Figure 2.

TTP in patients receiving first-line therapy according to GPS

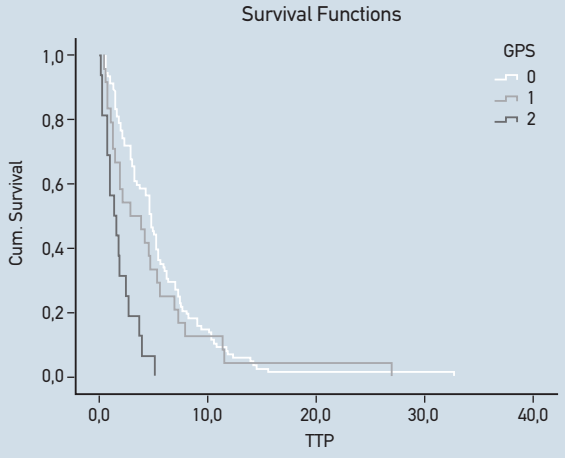
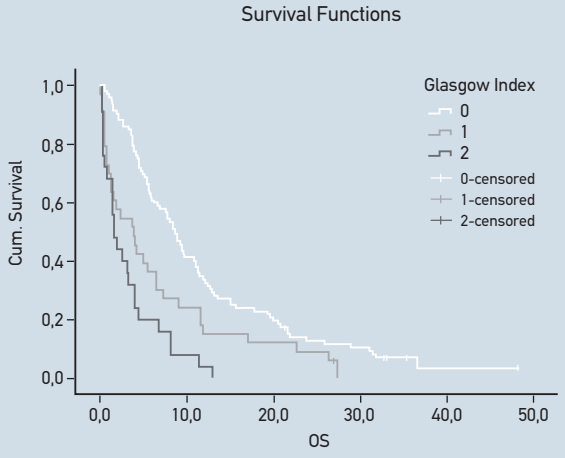


Figure 3.

OS in patients receiving first-line therapy according to GPS



factors in both univariate and multivariate analyses. Age (p=0.06) and BMI (p=0.06) were on the borderline of statistical significance in univariate analysis (Tables 2 and 3).

DISCUSSION

Systemic inflammatory response markers represent reliable tumor stage independent prognostic factors in patients with advanced cancer (4-8). GPS, which represents the combination of C-reactive protein and albumin into a score (0, 1, 2), is being proposed as a tool for survival prediction independent of tumor stage, performance status and treatment (active or palliative), in a variety of advanced common solid tumors (5). Moreover, GPS is directly associated with elevated cytokine and adipokine concentrations; biochemical disturbance; the loss of weight and lean tissue; and deterioration of performance status supporting its relation with cancer cachexia (23, 27, 28). In the present study we have confirmed the relation of GPS to BMI and weight loss history.

Forrest *et al.* tested the prognostic value of GPS in 107 patients with advanced NSCLC receiving first-line platinum-based chemotherapy and the reported median survival was 17, 12 and 7 months for Groups 0, 1 and 2, respectively (12). This difference was statistically significant for this relatively homogeneous population of patients in terms of histological type and treatment received.

We have explored the predictive and prognostic value of GPS in newly diagnosed Greek patients with metastatic lung cancer, irrespectively of histological subtype. Most of the accrued patients belonged to Group 0, indicating a good prognosis. GPS was correlated with both the PS and the number of metastatic sites. For those patients who received some form of first-line chemotherapy, GPS was significantly related to ORR, TTP and OS. In addition, for the total cohort of patients, GPS could

Table 2.
Univariate analysis for TTP and OS

		Time to Tumor Progression		Overall Survival	
Factor	**Groups**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Sex	Females vs. Males	0.790 (0.47-1.32)	0.37	0.96 (0.58-1.59)	0.87
Current smokers	Smokers vs. Ex/Never smokers	1.32 (0.87-2.0)	0.19	0.98 (0.67-1.42)	0.90
PS	≥2 vs. 0/1*	2.03 (1.41-2.92)	<0.01	3.33 (2.35-4.73)	<0.01
Weight loss	≥5% vs. <5%*	1.67 (1.17-2.40)	0.01	2.24 (1.59-3.17)	<0.01
Number of sites	≥2 vs. <2	1.35 (0.79-2.33)	0.27	1.45 (8.71-2.41)	0.15
Glasgow PS (primary)	B vs. A C vs. A*	1.24 (0.79-1.96) 4.21 (2.38-7.45)	0.35 <0.01	1.76 (1.17-2.65) 4.14 (2.57-6.66)	0.01 <0.01
Age		1.02 (1.01-1.03)	0.04	1.02 (1.00-1.03)	0.06
BMI		0.97 (0.93-1.00)	0.08	0.97 (0.93-1.00)	0.06

* favorable variable

Table 3.
Multivariate analysis for TTP and OS

		Time to Tumor Progression		Overall Survival	
Factor	**Groups**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
PS	≥2 vs. 0/1*	1.32 (0.86-2.01)	0.20	2.26 (1.53-3.34)	<0.01
Weight loss	≥5% vs. <5%*	1.53 (1.04-2.26)	0.03	2.30 (1.58-3.34)	<0.01
Glasgow PS (primary)	B vs. A* C vs. A*	1.50 (0.93-2.42) 3.20 (1.68-6.07)	0.10 <0.01	1.47 (0.93-2.34) 2.82 (1.69-4.70)	0.10 <0.01
Age		1.01 (0.99-1.03)	0.22		

* favorable variable

discriminate three different prognostic categories with distinct survival. Moreover, in the studied population, GPS emerged as an independent predictive and prognostic factor, as this was verified in the multivariate analysis.

Our results are not comparable to those of Forrest *et al.*, as this trial included a group of metastatic NSCLC patients with relatively good PS, exposed to platinum-based combination treatment (12). This lack of homogeneity may be one of the limitations of this study, although GPS did correlate with overall survival both in the total cohort and in those patients that received active treatment.

As could be expected, patients in the good GPS group were exposed to systemic therapy more frequently. More importantly, among treated patients, GPS was correlated to ORR and TTP. This difference could be partly explained by the alteration of the P450 3A cytochrome activity -the principal drug-metabolizing enzyme in a variety of chemotherapeutic agents- in the presence of a systemic inflammatory response. This may result to increased toxicity, dose reduction and treatment-related failure (29, 30). In our study, significantly more patients with adverse GPS discontinued treatment due to non-acceptable toxicity and this was in accordance to the data presented by Forrest *et al.* (12).

In conclusion, this is the first study examining the predictive and prognostic role of the GPS in Greek patients with metastatic lung cancer. GPS is a simple objective measure that reflects cachexia and reliably predicts outcome in cancer patients.

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Prevalence of metabolic syndrome among testicular cancer survivors: preliminary results from a prospective study

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ABSTRACT

Background: As testicular cancer (TC) is characterized by excellent prognosis, morbidity from treatment-related late metabolic effects, including obesity, hypertension, dyslipidemia and insulin resistance (all together constituting the so-called metabolic syndrome) is becoming an issue of major concern among TC survivors.

Patients & Methods: From 2001 to 2009 we prospectively evaluated all TC survivors (N=70) in our department after treatment completion and every six months thereafter for metabolic syndrome components, including waist circumference, body mass index (BMI), serum fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Levels of serum total testosterone, estradiol, luteinizing hormone (LH) and follicular-stimulating hormone (FSH) were also assessed for their correlation with metabolic syndrome.

Results: After a median observation time of 5.1 years, eight patients (11.4%) met the criteria for metabolic syndrome diagnosis. Significantly more men in the group that received chemotherapy were diagnosed with metabolic syndrome compared to the non-chemotherapy (orchiectomy ± radiotherapy) group (8 out of 58 compared to zero out of 12, $p<0.001$). Hypertriglyceridemia, low HDL levels and high fasting glucose levels were diagnosed in 31.4%, 25.7% and 17.1% of the patients, respectively. Mean BMI was 26.7 with BMI >30 in 20% of the patients; and waist circumference >105 cm was measured in 25.7% of the patients. There was no association between low testosterone or high estradiol/FSH/LH levels and metabolic syndrome prevalence.

Conclusion: Preliminary results in this small prospective cohort confirm an increased prevalence of cardiovascular risk factors that constitute the metabolic syndrome among TC survivors.

Key words: testicular cancer; platinum-based chemotherapy; metabolic syndrome; cardiovascular risk factors.

INTRODUCTION

With a constantly increasing incidence, testicular cancer (TC) has become the most common malignancy among men between the ages of 20 and 40 (1). With the development of highly effective chemotherapy, patients with advanced disease have an excellent chance for cure. Consequently, the number of long-term TC survivors is increasing and morbidity from treatment-related late side effects is becoming an issue of major concern (2). The first reports on the long-term follow-up of testicular cancer patients, including late treatment-related toxicity report, originate in the late 1980s (3).

A key concern refers to cardiovascular events, in particular myocardial infarction and coronary artery disease, after treatment with cisplatin-based chemotherapy, which has become the standard of care over the past two decades. With prolonged follow-up and a growing number of these survivors, there is accumulating evidence that both chemotherapy and radiotherapy are associated with an increased long-term risk of cardiovascular events (4-6). Possible mechanisms include endothelial dysfunction with early atherosclerosis and disrupted platelet-endothelial adhesion caused by direct endothelial damage from free-radical formation in the vascular micro-environment (7).

In parallel with direct endothelial toxicity, several studies on long-term complications have focused on the prevalence of cardio-

vascular risk factors, particularly dyslipidemia, obesity and hypertension (8-11). Together with insulin resistance, these risk factors constitute the basic characteristics of the so-called metabolic syndrome (3). The high incidence of these cardiovascular risk factors in testicular cancer survivors has lead to the concept that there may be increased metabolic syndrome prevalence in this group of patients (12). This association has rendered the diagnosis of metabolic syndrome a useful tool in the effort to identify people at increased risk for major cardiovascular events and a target for therapeutic approaches in clinical practice (3). In this study, we aimed at evaluating metabolic syndrome prevalence among TC survivors in a prospective fashion in order to identify individuals at increased risk for major cardiovascular events.

PATIENTS & METHODS

From 2000 to 2009, patients under 50 years of age with a histological diagnosis of primary testicular cancer were prospectively evaluated. After treatment (surgery or chemotherapy or radiotherapy or combinations), all subjects were put under medical surveillance in the outpatient oncology clinic and had to be free of disease at the time of initial evaluation. The study was approved by the Institutional Review Board and informed consent was obtained from each participant. Patients were categorized into four treatment groups: surgery only, radiotherapy only, chemotherapy with a cumulative dose of cisplatin <850 mg and chemotherapy with a cumulative dose of cisplatin >850 mg, since the latter dose refers to patients whose chemotherapy exceeds four cycles of treatment due to advanced or refractory disease, disease progression or relapse (13).

For each subject, clinical data such as age at diagnosis, family status, physical activity and smoking habits were recorded and information regarding the use of antihypertensive, anti-diabetic and/or lipid-lowering medication was obtained. All patients underwent clinical evaluation at completion of treatment modalities (baseline) and every six months thereafter, including body weight (in kilograms), blood pressure (in mmHg) and waist circumference (in cm). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Resting blood pressure was measured manually in both hands and the highest value was recorded. Blood samples were drawn post treatment (baseline) and every six months thereafter to assess the levels of serum fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Levels of serum total testosterone, luteinizing hormone (LH) and follicular-stimulating hormone (FSH), as well as thyroid function (T3, T4 and thyroid-stimulating hormone or TSH) were also determined at baseline and every six months thereafter.

For the definition of metabolic syndrome the 2008 American Heart Association criteria were used (14): Hypertension was defined as blood pressure levels above 130 and 85 mmHg for the systolic and/or diastolic component respectively. Body mass index (BMI) values more than 30 and/or waist circumference values more than 102 cm were used as a surrogate marker for obesity (14). Dyslipidemia was defined either as total cholesterol levels more than 240 mg/dl or triglyceride levels more than 150 mg/dl or HDL levels less than 40 mg/dl or the use of lipid-lowering drugs. For the detection of hyperglycemia, the cut-off point of 120 mg/dl in blood fasting glucose or the use of anti-diabetic medication

Table 1.

Basic clinicopathological characteristics in the follow-up examination

Characteristic	N (%)
Age at follow-up, years	
Mean	34.2
Range	23.4-50.0
Observation time, years	
Mean	5.1
Range	0.5-9.7
BMI at follow-up	
Mean	26.7
Range	22.0-35.0
BMI >30 (%)	14 (20%)
TNM (1997) stage, diagnosis	
I	46 (65.6%)
II	12 (17.2%)
III	12 (17.2%)
Histology	
Nonseminoma	32 (45.7%)
Seminoma	34 (48.5%)
Sarcoma	1 (1.4%)
Mixed	3 (4.4%)
Type of treatment	
Orchiectomy	70 (100%)
Radiotherapy	6 (8.6%)
Chemotherapy	58 (82.9%)
Platinum doses	
Cisplatin <850 mg	52/58 (89.7%)
Cisplatin >850 mg	6/58 (10.3%)
Parental status	
Married with children	43 (61.4%)
Single	24 (34.3%)
Unknown	3 (4.3%)
Smoking at diagnosis	36 (51.4%)

was used. For the diagnosis of metabolic syndrome, coexistence of three or more of the aforementioned components was required (14).

Data were analyzed using the SPSS statistical software (version 13.0). For each component of the metabolic syndrome, mean and median values were calculated and metabolic syndrome prevalence within each patient group was estimated. Differences between the mean and median values for each parameter between the study groups were calculated using the chi-square test for parametric variables and the Wilcoxon non-parametric test for continuous variables (e.g. waist circumference).

RESULTS

From 2000 to 2009, eighty-two (N=82) eligible patients have been prospectively evaluated, among which seventy (N=70) patients have completed evaluation for metabolic syndrome components at baseline and at least once during the follow-up period. The median observation time was 5.1 years from diagnosis (range: 1-9 years). Histological type was nonseminoma in 32 (45.7%) patients and pure seminoma in 34 (48.6%) patients. Forty-six (65.7%) patients were diagnosed as stage I according to the TNM 2007 classification. Orchiectomy was performed in all cases; six (8.6%) patients underwent radiotherapy only and 58 (82.9%) received chemotherapy. Total cumulative cisplatin doses were >850 mg in 6/58 (10.3%) patients that received chemotherapy.

Mean patient age in the follow-up evaluation was 34.4 years (range: 24-51). Mean values for the various study parameters are presented in Table 1. Twenty-two patients (31.4%) had hypertriglyceridemia according to the study protocol. HDL levels below 40 mg/dl were detected in eighteen (25.7%) patients, whereas fasting glucose levels >120 mg/dl were reported in twelve (17.1%) patients. Four patients (5.7%) have been diagnosed with diabetes mellitus and there was no documented major cardiovascular event. Four (5.7%) patients have been receiving medication for arterial hypertension and 24 (34.3%) were active cigarette smokers. Regarding obesity, mean BMI upon follow-up evaluation was 26.7 (range: 22-35) with BMI >30 in fourteen (20%) patients, and waist circumference >105 cm was measured in eighteen (25.7%) patients at the same time.

According to the aforementioned criteria, metabolic syndrome was diagnosed in eight (11.4%) patients whereas at least one component of the syndrome was present in 42.9% of the patients and ≥2 components in 20% (14/70) of the patients (Table 2). None of the patients that were diagnosed with metabolic syndrome belonged to the radiotherapy-only or orchiectomy-only group. Consequently, significantly more men in the group that received chemotherapy were diagnosed with metabolic syndrome compared to the non-chemotherapy (orchiectomy ± radiotherapy) group ($p<0.001$). Hormonal status assessment revealed low testosterone levels in eight patients (11.4%). Increased serum levels of FSH and LH were detected in 14 (20%) and 2 (2.9%) patients, respectively, whereas increased estradiol levels were detected in eight (11.4%) patients. Six patients that had low testosterone levels (among which four had also high estradiol levels) had an affected sperm diagram in terms of semen density or sperm motility and four of them that were married reported fertility issues.

No association was demonstrated with variables known to predispose to the development of metabolic syndrome such as testosterone levels, physical activity, treatment modality and total cisplatin doses. Interestingly, in univariate analysis,

Table 2.
Components of the metabolic syndrome

Metabolic syndrome component	N (%)	Mean value (range)
Waist circumference >105 cm	18 (25.7%)	96.7 (78-117)
Fasting glucose >120 mg/dl	12 (17.1%)	95.18 (70-184)
Triglycerides >150 mg/dl	22 (31.4%)	137.2 (41-298)
HDL cholesterol <40 mg/dl	18 (25.7%)	43.9 (21-68)
Arterial hypertension (>120/80 mmHg)	4 (5.7%)	
Metabolic syndrome		
≥1 components	30 (42.9%)	
≥2 components	14 (20.0%)	
≥3 components	8 (11.4%)	
≥4 components	2 (2.9%)	

increased odds for metabolic syndrome were found for those patients diagnosed at stage IV of the disease (HR: 1.71, 95% CI: 1.19-2.87, p=0.025), for those with age more than 35 years at diagnosis (HR: 1.66, 95% CI: 1.11-2.24, p=0.031) and for single men (HR: 1.42, 95% CI: 1.07-1.91, p=0.035).

DISCUSSION

In this study, cisplatin-treated testicular cancer (TC) survivors show an increased age-adjusted risk of developing metabolic syndrome as compared to those treated with surgery or radiotherapy alone. The increased prevalence of risk factors for cardiovascular disease has been long recognized as a potentially hazardous effect of platinum-based chemotherapy, following the accumulated experience of long-term follow-up in TC survivors (15). There is increasing evidence that platinum-based chemotherapy, which represents the cornerstone for the treatment of these tumors, is associated with an increased long-term risk of cardiovascular disease, mainly due to the high prevalence of metabolic syndrome components, which at the same time represent important risk factors for the occurrence of major cardiovascular events, such as unstable angina or myocardial infarction (16).

We found that practically one out of five TC survivors is obese according to the BMI WHO criteria and one out of four patients has an increased waist circumference during the follow-up evaluation. Moreover, almost one third of TC survivors has an increased triglyceride level and one out of four has a decreased HDL level. These results come in accordance with numerous other reports emphasizing the increased prevalence of metabolic syndrome among TC survivors. In one of the largest retrospective cohorts reported to date, originating from the Norwegian cancer registry, the authors concluded that TC survivors treated with platinum-based chemotherapy have an increased risk for developing metabolic syndrome and consequently experiencing major cardiovascular events (13). Recently, the same investigators reported on the extended follow-up of the same patient cohort that reached 19 years (median observation time) (17). In this updated report on 990 TC survivors, the authors found an increased prevalence of antihypertensive medication, diabetes mellitus, atherosclerotic disease, coronary artery disease and myocardial infarction in chemotherapy-treated patients compared to age-matched male controls from the general population (17). Similar results have been generated from smaller retrospective studies [Reviewed in (18)]. The current study is also limited by the small number of patients; however, its prospective design allowed the pre-planned evaluation of sex-related hormone levels in parallel with the components of metabolic syndrome and the sufficient follow-up time (of five years) offers an adequate median observation period.

Chemotherapy-related cardiovascular toxicity is probably the result of both direct endothelial damage induced by cisplatin and indirect hormonal and metabolic changes. It has been suggested that the increased incidence of metabolic syndrome in TC survivors is most likely associated with the lower testosterone levels reported (18). Today, it is well-established that platinum compounds affect not only Leydig cells but also Sertoli and germ-cells, resulting in various levels of infertility in 30-50% of patients treated with chemotherapy (20). Low serum testosterone levels have also emerged as an important prognosticator of metabolic syndrome prevalence in men whose testosterone deficiency is genetic (Klinefelter syndrome); iatrogenic following surgery for testicular cancer; pharmacological induced by gonadotrophin-releasing hormone during prostate cancer treatment; or as a natural consequence of aging (20). In the current report we confirmed the increased incidence of low testosterone levels (and high FSH and estradiol levels) among TC survivors but we were not able to establish any association between low testosterone or high FSH/estradiol levels and metabolic syndrome incidence, probably due to the limited number of patients in our cohort. However, it is of note that in our cohort four out of eight patients with low testosterone levels and five out of 14 patients with high FSH levels developed metabolic syndrome, an observation that underlines the interaction between sex-related hormones and metabolic syndrome components.

In the aforementioned Norwegian study (13), TC survivors that received high cumulative doses of cisplatin (>850 mg) had increased odds (OR=2.1) for developing metabolic syndrome compared to the control group and this association was enhanced after adjusting for testosterone levels, smoking, physical activity, education and family status (13). The direct relationship between chemotherapy and metabolic syndrome prevalence is further supported by the fact that only platinum-based chemotherapy has been associated with the development of atherogenic lipid changes, increased serum cholesterol, dyslipidemia, obesity, insulin resistance and hypertension, while radiation treatment is followed by elevated levels of chronic inflammation and endothelial dysfunction serum markers (20). Again, in our cohort, the insufficient statistical power did not allow the detection of correlations between cumulative platinum dose, smoking, obesity, or lack of physical activity and metabolic syndrome prevalence. Nevertheless, we observed that all but one of the eight patients that developed metabolic syndrome were active smokers at the time of evaluation; six of them were obese according to the BMI WHO criteria; and all of them reported lack of physical activity.

In conclusion, our prospective evaluation on a small cohort of patients after 5 years of observation supports the mounting evidence for an increased prevalence of metabolic syndrome among TC survivors that received platinum-based chemotherapy. The direct association between the cumulative platinum dose or testosterone levels and metabolic syndrome prevalence could not be established

because of the limited number of patients and the lack of major cardiovascular events in our cohort. However, continuing accrual of patients and observation time prolongation that will allow recording of all cardiovascular events is expected to allow safer conclusions to be drawn and is currently ongoing.

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The Lapatinib plus Capecitabine combination safety profile in patients with HER2-positive advanced breast cancer: the Metropolitan experience in 27 patients

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ABSTRACT

Background: Effective treatment options for patients with metastatic breast cancer resistant to anthracyclines, taxanes and Trastuzumab are limited. Lapatinib, an oral tyrosine kinase inhibitor, targeting both the human epidermal growth factor receptor type 2 (HER2) and epidermal growth factor receptor (EGFR), is active in combination with Capecitabine in women with HER2-positive advanced breast cancer.

Patients & Methods: We retrospectively reviewed data from 27 patients treated with Lapatinib at a dose of 1250 mg per day continuously plus Capecitabine at a dose of 2000 mg per square meter of body surface area on days 1 through 14 of a 21-day cycle from June 2007 to January 2010. The purpose was to assess the safety and efficacy of the 21-day schedule of Lapatinib plus Capecitabine in a non-selected population, as applied in the everyday practice of our department.

Results: It is of interest that this group of patients was highly pretreated with taxanes (100%), anthracyclines (74%), trastuzumab (81%) and other chemotherapeutic drugs. They had received median 4 prior lines of chemotherapy for metastatic breast cancer. Complete response (CR) was achieved in 2 patients (8%), partial response (PR) in 9 (33%) and stable disease (SD) in 3 (11%). The most common adverse events were diarrhea; vomiting; hand and foot syndrome; fatigue; and rash. Most adverse events were grade I and II. Grade III toxicities included diarrhea (11%), fatigue (4%), hand and foot syndrome (8%), vomiting (4%) and disequilibrium (4%). No toxic death occurred.

Conclusion: The 21-day schedule was effective and well tolerated in heavily-pretreated women with HER2 positive advanced breast cancer.

Key words: breast cancer; HER2; capecitabine; lapatinib.

Acronyms

HER2:	human epidermal growth factor receptor type 2
EGFR:	epidermal growth factor receptor
FDA:	Food and Drug Administration
RECIST:	Response Evaluation Criteria in Solid Tumors

Breast cancer is still the most frequent type of cancer and the second cause of death from cancer in women, after lung cancer, in many countries, including developing ones (1). However, no standard of care exists for subsequent lines of chemotherapy, particularly after failure of both anthracyclines and taxanes, and treatment options for these patients are limited (2). On March 13 2007, Lapatinib, an orally active small molecule that inhibits the tyrosine kinases of human epidermal growth factor receptor type 2 (HER2) and epidermal growth factor receptor type 1 (EGFR), was approved by the Food and Drug Administration for use in combination with Capecitabine for the treatment of patients with HER-2-overexpressing metastatic breast cancer who had received prior therapy including an anthracycline, a taxane, and trastuzumab (3, 4, 5). From June 2007 to

January 2010, 27 heavily pre-treated women with HER-2 positive advanced breast cancer received treatment with Lapatinib plus Capecitabine in our clinic. We retrospectively reviewed data from these patients in order to assess the safety and efficacy of the schedule.

The HER2 status was considered positive if the local institution reported grade 3+ staining intensity (on a scale of 0 to 3) as assessed by immunohistochemical analysis or grade 2+ staining intensity with gene amplification on fluorescence in situ hybridization (FISH).

Patients were receiving Lapatinib (1250 mg once daily on days 1-21) plus Capecitabine (1000 mg/m^2 every 12 hours on days 1-14) every 21 days.

All patients had baseline computed tomography or magnetic resonance imaging of the chest and abdomen. Radiographic response and serum tumor markers were evaluated every 12 weeks or earlier if there was a clinical suspicion of progression. Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST). Adverse events were graded using the NCI Common Toxicity Criteria version 3.0 at baseline and every course of therapy. Criteria for treatment discontinuation included severe drug-related toxicity, progressive disease or change in patient's condition that made further treatment inappropriate.

Baseline patient and treatment characteristics of the population included in this study are presented in Table 1. The median age of the 27 patients analyzed was 50 years (ranging from 32 to 70). They had metastatic breast cancer that had progressed after treatment with regimens that included taxanes (100%); Trastuzumab (81%); anthracyclines

Table 1.

Baseline characteristics of the 27 women

Characteristic	Lapatinib plus Capecitabine (N=27)
Age – yr	
Median	50
Range	32-70
ECOG performance status – no. %	
0	18 (67%)
1	7 (26%)
Unknown	2 (8%)
Hormone receptor status – no. %	
Positive for estrogen receptor	17 (63%)
Negative for estrogen receptor	9 (33%)
Missing data for estrogen receptor	1 (4%)
Positive for progesterone receptor	13 (48%)
Negative for progesterone receptor	13 (48%)
Missing data for progesterone receptor	1 (4%)
Positive for estrogen receptor, progesterone receptor or both	18 (66%)
Negative for estrogen receptor and progesterone receptor	8 (30%)
Missing data for estrogen receptor, progesterone receptor	1 (4%)
Stage of disease – no. (%)	
Metastatic	27 (100%)
No. of advanced or metastatic sites – no. (%)	
≥3	13 (48%)
2	5 (19%)
1	9 (33%)
Advanced or metastatic sites – no. (%)	
Visceral only	8 (30%)
Visceral and non-visceral	15 (55%)
Non-visceral only	4 (15%)

Table 1. (suite)

Previous therapy – no. (%)	
anthracyclines	20 (74%)
taxanes	27 (100%)
Fluorouracil	14 (52%)
Vinorelbine	12 (44%)
Trastuzumab	22 (81%)
Cyclophosphamide	19 (70%)
platines	12 (44%)
Methotrexate	13 (48%)
Doxorubicin	4 (15%)
Gemcitabine	5 (19%)
Temozolomide	1 (4%)
Mitomycin	1 (4%)
Adjuvant therapy	20 (74%)
Neoadjuvant therapy	0
For metastatic disease	25 (93%)
Lapatinib plus Capecitabine as 1st line chemotherapy	2 (8%)
Previous chemotherapy lines – no. (%)	
1	5 (19%)
2	5 (19%)
3	1 (4%)
4	3 (11%)
5	8 (30%)
6	1 (4%)
10	1 (4%)
Duration of Lapatinib plus Capecitabine therapy – wk	
Mean	32
Range	6-121
Duration of Lapatinib plus Capecitabine therapy – no. (%)	
<12 wk	6 (22%)
12-24 wk	10 (37%)
>24 wk	11 (41%)

(74%); Cyclophosphamide (70%); Fluorouracil (52%); Methotrexate (48%); Vinorelbine (44%); Platinum (44%); Gemcitabine (19%); Temozolamide (4%); and Mitomycin (4%).

All the patients were HER-2 positive. Eighteen women (66%) were positive for estrogen receptor, progesterone receptor or both and eight women (30%) were negative.

All the patients had measurable disease. Thirteen of them (48%) had more than three metastatic sites; five (19%) had two; and nine (33%) had one site. Eight (30%) had visceral metastases; four (15%) had non-visceral metastases; and fifteen (55%) had both visceral and non-visceral metastases.

Their performance status was 0 (67%) or 1 (26%) according to the Eastern Cooperative Oncology Group. Their cardiac ejection fraction was within the institutional normal range and their laboratory function was adequate. Twenty of them (74%) had received adjuvant chemotherapy and twenty five of them (93%) received chemotherapy for metastatic disease. The median of chemotherapy lines, before starting to receive Lapatinib plus Capecitabine, was 4.

Between June 2007 and January 2010, twenty seven patients were treated with the 21-day schedule of Lapatinib and

Table 2.
Efficacy End Points

End Point	Lapatinib plus Capecitabine (N=27)
Median time to progression - wk	24 weeks
Complete Response - no. (%)	2 (8%)
Partial Response - no. (%)	9 (33%)
Stable Disease - no. (%)	3 (11%)
Clinical Benefit - no. (%)	14 (52%)

Table 3.
Adverse Events

Event	Lapatinib plus Capecitabine (N=27)				
	All grades	Grade I	Grade II	Grade III	Grade IV
Diarrhea	17 (63%)	11 (41%)	6 (22%)	3 (11%)	0
Nausea	1 (4%)	1 (4)	0	0	0
Vomiting	2 (8%)	2 (8%)	0	1 (4%)	0
Stomatitis	3 (11%)	3 (11%)	0	0	0
Nail changes	4 (15%)	3 (11%)	1 (4%)	0	0
Rhinitis	3 (11%)	3 (11%)	0	0	0
Blepharitis	1 (4%)	1 (4%)	0	0	0
Hand and foot syndrome	13 (48%)	8 (33%)	4 (15%)	2 (8%)	0
Rash	5 (19%)	5 (19%)	1 (4%)	0	0
Dry skin	2 (8%)	2 (8%)	0	0	0
Fatigue	14 (52%)	12 (48%)	2 (8%)	1 (4%)	0
Light sensitivity	1 (4%)	1 (4%)	0	0	0
Abdominal flatulence	1 (4%)	1 (4%)	0	0	0
Anorexia	2 (8%)	2 (8%)	0	0	0
Somnolence	1 (4%)	1 (4%)	0	0	0
Alopecia	1 (4%)	1 (4%)	0	0	0
Neuropathy (sensory)	4 (15%)	4 (15%)	0	0	0
Tinnitus	1 (4%)	1 (4%)	0	0	0
Disequilibrium	1 (4%)	0	0	1 (4%)	0
Cervicodynia	1 (4%)	1 (4%)	0	0	0

Capecitabine at our department. All patients were included in this analysis and represented an unselected population. The mean duration of treatment was approximately 32 weeks (ranging from 6 to 121). Complete response (CR) was achieved in 2 patients (8%); partial response (PR) in 9 (33%); and stable disease (SD) in 3 (11%) (Table 2). Four patients remain on active treatment and five patients died because of disease progression at a median time of 6 months after discontinuation of the Lapatinib plus Capecitabine combination and while they had received other treatments.

No unexpected toxicities were observed. Treatment-related adverse events were mostly grade I or II and generally reversible. Table 3 summarizes the incidences of treatment-related adverse events. The most common adverse reactions during therapy with Lapatinib plus Capecitabine were gastrointestinal (diarrhea 63%, nausea 4%, vomiting 8%) or dermatological, such as hand and foot syndrome (48%) and rash (19%). Fatigue was noted in 52% of patients and stomatitis occurred in 11%. The most common grade 3 adverse reactions for the Lapatinib and Capecitabine combination were diarrhea (14%) and hand and foot syndrome (12%). Grade III toxicities included diarrhea (11%), fatigue (4%), hand and foot syndrome (8%), vomiting (4%) and disequilibrium (4%). No grade IV toxicity or toxic death occurred and none of the patients discontinued treatment because of adverse events. Most of the adverse events, such as diarrhea, hand and foot syndrome, stomatitis and dry skin are expected, according to the literature (4, 5). Some others were presented at a lower percentage, such as nausea, rash and anorexia, though fatigue was observed in a higher frequency. Finally, we noticed new toxicities, which included nail changes, rhinitis, blepharitis, alopecia, neuropathy sensory and disequilibrium which probably occurred due to the medical history of heavily pretreated women. At the end of the treatment the left ventricular ejection fraction did not significantly decline. No cardiac events were identified.

This retrospective study assesses the safety and efficacy of the 21-day schedule of Lapatinib plus Capecitabine in a non-selected population of heavily pretreated HER-2 positive patients with metastatic breast cancer. The analysis showed that this combination is effective and well tolerated. Grade 3 and 4 toxicities are rare, and most adverse events associated with this schedule are of grade 1 or 2 in severity. The incidence of adverse events commonly associated with Capecitabine, such as hand-foot syndrome, was not exacerbated by the addition of Lapatinib. Therefore, this group of patients which had already received a median of 4 lines of chemotherapy derived a clinical benefit from the above treatment.

These results are consistent with the findings of other studies and provide support for the use of Lapatinib and Capecitabine in this group of women (4, 5). Geyer *et al.* showed the clinical activity of Lapatinib in HER2-positive breast cancer and the superiority in the 21-day schedule of Lapatinib plus Capecitabine in comparison to Capecitabine alone. Their study population was carefully selected and included women with HER2-positive locally advanced or metastatic breast cancer that had progressed after treatment with anthracyclines, taxanes and Trastuzumab.

Even though our retrospective study included a non-selected and more heavily pre-treated population of patients, the combination of Lapatinib with Capecitabine was active and well tolerated.

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Establishing a Radiotherapy Department for treating children with malignancies - an opinion sample of radiation oncologists and radiation physicists on the radiotherapy requirements for children

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ABSTRACT

Background: Delivering radiotherapy to children with malignancies is a highly specialized task. The purpose of this study was to investigate current practice for stuff and equipment.

Patients & Methods: Interviews regarding the current practice in staffing and selecting the equipment for a pediatric oncology unit were obtained from eleven radiation oncologists and radiation physicists and one social worker active in this field.

Results: The conclusions drawn by interviewing this limited number of scientists can be summarized as follows: a. The most important aspect of pediatric oncology is staff dedicated to and knowledgeable of pediatric radiation oncology; b. The technology for radiation oncology that will improve our treatment results and diminish late side-effects is clearly derived from the adult sphere, as the developments in treatment planning and treatment techniques are best based upon a far larger number of patients; c. It would be ideal to install a complete radiation oncology department with everything it entails in the average children's hospital. The reason that such an arrangement would be ideal is that all the facilities and personnel familiar with the management of children would be immediately available. The next best solution is a radiation oncology facility connected to a children's hospital. This way, the advantages of having the pediatric personnel very close is gained, while not sacrificing the economy and efficiency gained by using the services of a complete radiation therapy department, which is needed for the much larger number of adult patients.

Conclusions: The conclusions drawn from this study may prove to be useful to health professionals in general, particularly in countries where facilities for treating children with cancer are under development. This generation of radiation oncologists is required not only to treat children with cancer more accurately and efficiently, but also to closely follow-up the survivors in order to determine late side-effects -particularly secondary cancers.

Key words: pediatric oncology; radiotherapy; personnel; equipment.

INTRODUCTION

Worldwide mortality data demonstrate that cancer in the pediatric age group (below 18 years old) is second only to accidents as the leading cause of death; although approximately 70% of children diagnosed with cancer today are expected to survive for five or more years. Over the past four decades, we have experienced the development of new approaches to radiation and surgical oncology, new chemotherapeutic agents, and an enormous improvement in diagnostic and supportive techniques, with special reference to magnetic resonance imaging. Radiotherapy still plays an important role in the management of children with malignant diseases, mainly in combination with other anti-cancer treatments. Delivering radiotherapy to children with malignancies still presents a highly-specialized task that poses many difficulties. It is in this challenging clinical situation that pediatricians, along with family practitioners and physicians in general, should be well-informed on the current status of treatment options availability.

The purpose of this study was to investigate the existing practice in staffing and selecting

the appropriate equipment for a pediatric oncology unit. Interviews from eleven world-wide experienced radiation oncologists and radiation physicists and one social worker were obtained using a sensitive questionnaire. Our effort was to provide health professionals and decision-makers in Greece with this state-of-the-art information concerning the establishment of such a specialized unit. We believe that the information contained herein will help other countries in the Balkan region to plan and execute such a challenging exercise.

PATIENTS & METHODS

One of the authors (CK) visited a number of Radiotherapy Departments specializing in the treatment of children in the U.S.A., Canada and Europe and interviewed specialists, Radiation Oncologists and Radiation Physicists (Table 1). The scope of these visits was the collection of information concerning the structure, flowchart, personnel and equipment needed for the creation of a high-standard department of radiation oncology in Greece, specializing in

Table 1.
Participants

Cunningham John, Ph.D.	"Theratronics Ltd", Kanata, Canada
D' Angio J. Giulio, M.D.	Medical Oncology Dept. Philadelphia Children's Hospital Philadelphia, U.S.A.
Jenkins Derrick, M.D.	Director, Radiation Oncology Dept., Toronto Regional Cancer Centre, Bayview, Canada
Habrand Jean-Louis, M.D.	Radiation Oncology Dept., Institut Gustave Roussy, Villejuif, France
Kun E. Larry, M.D.	Chairman, Radiation Oncology Dept., St. Jude Children's Research Hospital, Memphis, Tennessee, U.S.A.
Kutcher J. Gerald, Ph.D.	Radiation Physicist, Memorial Sloan Kettering Cancer Center, New York, N.Y., U.S.A.
Macliss Roger, M.D.	Deputy Div. Chief, Children's Hospital, Radiation Oncology Dept., Boston, U.S.A.
Palta R. Jatinder, Ph.D.	Director Physics Division, St. Jude's Children's Res. Hospital, Memphis Tennessee, U.S.A.
Schweisguth Odile, M.D.	Pédiatre - Oncologue, "Cotapre", Molphey, Saulieu, France
Theriault Claudine, M.D.	Radio-Oncologue, Hospital Notre Dame, Montreal Quebec, Canada
Rosenwald Jean-Claude, Ph.D.	Directeur Département de Physique Médicale, Institut Curie, Paris, France
Ziongas Theodora, Ph.D.	Social worker, Memorial Sloan Kettering Cancer Center, New York, N.Y., U.S.A.

Table 2.
Questionnaire

- Relating to radiotherapy, what is the age range of a "child"?
- Is the installation of a radiotherapy department in a children hospital worth the money and the effort? Do you think that radiotherapy for children could be as well-performed in general hospital?
- What kind of personnel should be associated with a children's (paediatric) radiotherapy department?
- Should one person be mainly responsible for the patient and accordingly perform all the necessary procedures?
- What kind of treatment machines are needed for child radiation therapy?
- What is needed for performing total body irradiation on children?
- What means of immobilization techniques are used for children?
- Which recent technological developments in Radiotherapy (i.e. 3-D Imaging, Conformal Therapy, Multileaf Collimators etc.) do you think would be valuable for the treatment of children and why?

the treatment of childhood cancer. An important aspect of these discussions was the dilemma of establishing such a department either in a children's hospital or in an adult's general hospital.

A questionnaire was drawn up and the answers were analyzed and grouped by the authors (Table 2).

RESULTS

1. Relating to radiotherapy, what is the age range of a "child"?

According to Dr. Jeckins, children are those up to and including 16 years of age. According to Dr. Kun, in St. Jude Children's Research Hospital, doctors consider as children those up to and including 18 years of age (although they include in their treatment protocols adults to the age of twenty-five for bone tumors and, less often, for brain tumors). In general, oncologists regard a child as any cancer patient up to and including eighteen years of age, but if treatment complications do appear later, they consider this a pediatrics-related problem (Dr. Macliss).

2. Is the installation of a radiotherapy department in a children's hospital worth the money and the effort? Do you think that radiotherapy for children could be well-performed in a general hospital?

According to information collected from specialists in the U.S.A. and Canada, the tendency in North America is to have almost all pediatric cases referred to major radiotherapy centers. This is partly due to the fear of malpractice litigation later on.

In Canada, the specialists think that it is not right to divide the children between different radiotherapy centers, because in this way nobody receives the experience needed with children. So, radiation treatment facilities for children need to be regionalized and in this way, the Toronto Bayview Regional Cancer Centre for instance treats about 120 new children cases per year.

In the United States, the majority of Radiotherapy Centers treat children as follows:

- The majority of University Centers: 5-10 children / day
- 3-5 large radiotherapy centers: 10-12 children / day
- St. Jude's Children's Hospital: 15-20 children / day (200 new children / year)
- Los Angeles Children's Hospital: 15-20 children / day

In relation to the choice of where to establish a children's radiotherapy department, some general rules apply:

1. The most important aspect of a pediatric radiotherapy center is the availability of staff dedicated to and with knowledge of pediatric oncology. This raises the important point of including in radiotherapy trainee curriculum the opportunity to come in contact with radiotherapy-treated children.
2. The creation of a pediatric day-care unit, providing assistance right before the sessions; during irradiation for minor side-effects (infections, skin rashes etc.); and for the administration of sedatives or analgesics (Dr. Habrand).
3. It is extremely important to have close cooperation between the pediatric radiotherapy center and the children's hospital staff. This collaboration permits a constant exchange of information about their mutual patients and problems related to the disease and/or treatment.
4. During treatment simulation, doctors encourage the parents to assist, so that the patient feels comfortable and assured by their presence, which is then discouraged to avoid interference with the doctor's way of administering the treatment.

2.1. Based on data obtained, the following two solutions are proposed:

2.1.1. Installation of a radiotherapy center in a pediatric hospital

2.1.1.1. The needs of pediatrics patients and their families are very unique and they can only be addressed in a pediatric hospital, where physicians from all specialties are very sensitive to children's needs. Adult radiotherapy center staff dedicated to treating adults cannot treat children effectively without special training.

2.1.1.2. Contrary to the setting in an adult patients department, where patients have their privacy, the effort in children departments is to have patients and their relatives together in a more warm and relaxed environment where children can get support from each other. Some very sick children get the support they need from others. Sometimes, the ones who are very sick give more support to those who are less sick (Dr. Palta).

2.1.1.3. The small number of patients and the resulting flexibility of time offer such advantages as:

a. Children under the age of five that are scheduled for daily sedation during treatment and even if the whole sedation procedure takes an hour, this delay is anticipated and programmed and does not influence the normal flow of young patients.

b. The parents want everything to be done in exactly the right way, even if this means slowing down the entire schedule of the machine for the rest of the day.

c. For treating a child, the time needed can be on the average 2 to 2.5 times more than the time needed for treating an adult patient. In some cases this time is multiplied by a factor of three to four.

2.1.1.4. If this solution is chosen (children's hospital equipped with radiation therapy facilities), there should be only one per large city.

2.1.2. A radiotherapy center connected to a children's general hospital

This option requires special arrangements with a radiotherapy center for treating children by using 1 or 2 machines, at a specific time of day or to have a dedicated pediatric linear

accelerator(s). The latter has an advantage since the small number of patients allows a flexibility of time attributable to the problems of daily sedation cases. One should keep in mind that the normal turnover for adult patients is 15 min while for children 1 hour or more could be considered normal treatment time.

The radiotherapy center must be easily accessible and closely integrated with the children's hospital. Radiation Oncologists can visit the children's hospital to see new patients, discuss their care with the pediatricians and conduct follow-up clinics. This solution can address other important problems as well, such as following a school program (continuity of education) and playing in appropriate playgrounds.

In addition, in a large radiotherapy center, an entire range of apparatuses and support systems is available and a variety of professionals would acquire and maintain adequate skills to provide excellent care.

2.2. Clinical aspects of children radiotherapy

The areas particularly germane to pediatrics include:

2.2.1. Daily anesthesia. Many children require daily anesthesia, which is, at the time of simulation, a very important consideration because qualified and dedicated pediatric medical personnel are needed, especially when planning it.

2.2.2. Dose distribution. When treating adults with radiation, one of the most important topics is dose homogeneity; while treating children with radiation some dosimetric considerations are very specialized. Often, we have to divert the beam from a critical organ, without compromising the dose delivered to the tumor. In children radiotherapy, it is a general imperative to protect more the healthy tissues involved in treatment mainly due to smaller organ distances. In addition, some of the field configurations are unique to the pediatric service, e.g. cranio-spinal comprehensive central nervous system treatment. In these cases, utilized on average in about 25% of children with acute lymphoblastic leukemia, critically important are treatment techniques delivering the dose accurately and homogeneously. This procedure is the most technically demanding in a radiotherapy department; it is quite fine-tuned with specific casts and treatment techniques that are both time-consuming and precise.

The toxicity of pediatric radiotherapy is related, not only to all to those seen in adult cases, but also to the toxicity of all irradiating growing tissue. So, special techniques are used to prevent scoliosis or curvature of the bones later on development, which is never taken into consideration in adult radiotherapy.

In conclusion, as regards dose distribution, we very often sacrifice homogeneity to avoid late complications.

3. What kind of personnel should be associated with a children's (pediatric) radiotherapy department?

3.1. Radiation Oncologists, with a special interest in children's oncology, that are dedicated either full-time or with a primary academic interest in the treatment of children with cancer using radiotherapy are needed. They must be highly interactive with the pediatric medical team and the surgical oncology specialists, as well as neurosurgery and other referring physicians with whom very close cooperation is required. They must spend a lot of their time at the children's hospital (combined rounds each week).

3.2. A team of Radiation Physicists dealing with both routine clinical physics for treatment verification and complex dosimetry, as well as developmental research on three-dimensional imaging and treatment planning. This is particularly essential in idealizing the therapeutic ratio in pediatric radiation oncology. Among other duties, they must primarily assure that the machine is properly calibrated, since machine tolerances are much tighter. This is so because, for a pediatric patient, all organs and critical structures are scaled down and the "target volume" is much smaller. As Dr. Palta says "for an adult patient we may accept a machine which has a 2 mm tolerance, but for a pediatric patient you must accept the machine and maintain it with tighter tolerance".

3.3. Well-trained, specialized Nurses working both in the radiotherapy center and the children's hospital have to be recruited. Also, an important member of the staff is a well-trained sedation nurse conversant in dealing with children, and well-introduced to all aspects of radiation oncology, in order to specifically utilize sedation or work with an anesthesiologist during complex radiation treatments.

3.4. Senior Radiation Technologists and Dosimetrists experienced in treating children. This is very important, especially for fluoroscopic simulation, treatment planning, dosimetric analysis of the simulation films and preparing children. Technicians in the mould room do not need to have special training but are required to have high technical skills that allow them to customize the immobilization procedure.

3.5. Anesthesiologists. Anesthesia is delivered by an institutional anesthesiologist on a daily basis, often for several weeks and sometimes twice daily. It is critical that a trained sedation team is conversant in dealing with children and well-introduced to the aspects of radiation oncology in order to specifically utilize sedation or work with an anesthetist during complex radiation treatments.

3.6. Social service personnel that are not dedicated to radiation oncology but to the pediatric oncology unit in general and who work closely with the radiotherapy center. Social workers can solve the big problem of housing and transportation for both patients and parents. If they do not exist, then it is doctors or nurses who would have to spend all their time arranging such issues, which is practically almost impossible (Dr. Ziongas).

3.7. Nutritional support staff, capable of working both with oral nutritional supplements and gastric feeding tubes, as

well as intravenous hyper-alimentation on an outpatient basis as required.

4. Should one person be mainly responsible for the patient and accordingly perform all necessary procedures?

It is very important to have one doctor and perhaps one nurse to deal with the child and the parents. As Dr. Macliss stated "the reason I think that one doctor is best in dealing with the parents is that very often if there are only four or five children being treated at one time, all the parents get friendly and they know each other. And if the children are being treated according to different treatment philosophies, this is psychologically very difficult for the parents to understand. In our Department, even though my colleague and I each treat children, we have worked out standard uniform policies for all diseased, so that the patients would never get one answer from one of us and one answer from another. It would not be uncommon on the adult radiation of oncology service for a patient to be treated in one way from one physician and in another way from another physician.

Adults can sort of understand this. In kids, though, the parents become very upset when they hear that there might be other alternative ways and that no one knows what the right answer is. So I think it is best to have one person do the talking with all of the parents of all the children."

5. What kind of treatment machines are needed for child radiation therapy?

5.1. Simulator. The existence of a classic (fluoroscopic) or virtual (CT scanner-based) simulator is absolutely essential for pediatric patient localization. All the specialists agree on that, even in those departments with only one treatment machine.

5.2. Orthovoltage Unit. Specialists believe that treatment of superficial lesions can be performed adequately with electrons, using the same apparatus (cones) as for adults, so they do not require an orthovoltage unit. As Dr. Macliss emphasized "orthovoltage irradiation is absolutely not appropriate for children because of the differential attenuation in bone, and in growing bones, the last thing we want to use is orthovoltage." Dr. D'Angio has a different opinion and still uses an orthovoltage machine for palliative radiation therapy because it is readily available (not used very much) and "is perfectly adequate for the purpose intended in small children".

5.3. High Energy Photons. The choice of the appropriate treatment machine equally concerns the pediatric radiotherapy center as well as the adult department where children are admitted and a machine is a priority dedicated for them.

As Dr. Palta stated, it all depends on how many children are treated per year. Typically, in the United States, for every 250-300 patients, a linear accelerator is needed. Ideally, for pediatric patients this number has to be decreased by 2.5 times, because of the time; but even by 2 it's a workable situation. The ideal situation would be one machine for a hundred patients a year, with an ideal energy between cobalt-60 (cobalt unit) and 4MV.

Some of the experts interviewed do not recommend, yet accept the use of a cobalt unit for children (e.g. Drs. Cunningham, Rosenwald, Macliss and Jenkins). They believe that if there are serious cost considerations the cobalt unit may be chosen as, even if the penumbra is not optimal, it is acceptable. Because of the small separations in children and usually moderate doses, a cobalt unit is usually just about as efficient for many patients as high-energy machine (i.e. in irradiation for leukemia).

In contrary, Drs. Kun and Palta would not recommend using cobalt-60 for pediatric patients. And their reasoning is that the fields tend to be smaller because organs are smaller and this physical penumbra of the cobalt unit is significantly more than that of the linear accelerator. So normal tissues are overdosed, which could be avoided by treating the patient on a linear accelerator where the field edges are sharper, and new technology (such as IMRT and IGRT) could be implemented. The majority of Radiation Oncologists and Radiation Physicists very firmly believe that a low-energy (4MV) linear accelerator is the appropriate treatment modality in preference to the cobalt unit.

Consequently, as Drs. Palta and Jenkins stated, an ideal situation should be a dual photon energy machine of 4MV (majority of treatments) and 15MV MeV (for mid-line brain tumors). But for practical purposes, it's very difficult to have a machine with 4 and 15MV because there are no manufacturers producing them. So the compromise would be to have a 6MV and a 15MV dual energy accelerator (e.g. for brain cases: first course on a 6MV Linac and then localize dose just to the center part of the brain through two lateral fields - avoid overdose of the temporal lobes of the superficial part of the brain which cause long-term toxicity) (Dr. Macliss).

Various solutions proposed by Dr. Palta are presented below:

5.3.1. The ideal configuration is a two-machine setting to have a full complement of energies: A single photon energy machine of 4MV and a dual energy accelerator of 6 and 15MV and multiple electron energies.

5.3.2. A unique machine: A dual energy accelerator of 6 and 15MV and multiple electron energies.

5.3.3. Limited resources: An accelerator of 6 or 8MV and multiple electron energies (between 6 and 8 preference should be for 6MV but with very limited use of electrons).

5.3.4. Last solution: A cobalt unit.

5.4. Electron Therapy. According to specialists, electron therapy is rarely necessary in children. The main clinical needs include metastatic disease to the skin, lesions which are very close to some bones mass, testicular boost irradiation, posterior spinal component of cranio-spinal irradiation (instead of photons to limit the exit dose to the normal tissues) and in Wilm's tumor protocols (Dr. Palta). So, only one of the machines should have electron capability (Dr.

Jenkins). Dr. Palta suggests a complete series of energies up to 22MeV, or a maximum therapeutic depth of 6 to 7 cm to cover all ages of CSI patients. To obtain 20 or 22MeV electrons, one needs a high-energy machine (klystron driven) not a medium energy machine (magnetron driven).

5.5. Brachytherapy. Brachytherapy is not routinely used for children and, as Dr. Jenkins says, should not be used in children, because indications are very rare. So, as Dr. Macliss emphasizes, there is no need for a specialized pediatric brachytherapy expert and the few pediatric brachytherapy cases could be sent to another hospital. This is the case of St. Jude's Children Hospital (Dr. Kun). Through its university affiliation, they do provide brachytherapy, which is rarely used for non-rhabdo-myosarcomatous soft tissue sarcomas and for central nervous system tumors.

In this hospital, they apply brachytherapy using radioactive sources such as high activity iodine 125 seeds (in stereotactic brain implants to treat some of the recurrent brain tumors). For iodine 125 there is no need for special precaution as the energy is very low, and they have specially designed helmets which patients can wear so the family can stay with them for limited time. The patients stay restricted in room for a few days (Dr. Palta). A single cesium source (for nasopharyngeal tumors) is also used.

6. What is needed for performing Total Body Irradiation (TBI) on children?

An important condition for pediatric TBI is the well-defined technical requirements and consequently the calculation of the exact dose rate in the mid-plane of the patient. So, centers such as St. Jude's Children Hospital do not prefer the standing position across the room, but having the patient lying down on a couch which is longitudinally scanned under the beam. The reasons for this choice are:

6.1. When the patients come for total body irradiation, more often they are not in a good physical condition to stand up for treatment which lasts for about 30 minutes (including all the set-up and according to the protocol stipulation for a dose of 10cGy/min in the mid-plane and 175cGy / fraction). Lay the patient on platform, or a couch, and just linearly scan it under the beam.

6.2. This design of treatment allows them to change either the dose rate of the beam or the speed of the couch in such a way that a very uniform dose (within 10% maximum variation of dose) in the mid-plane of the patient can be obtained.

For some specialists, TBI is a declining technique in bone marrow transplantation (BMT) as regimens for transplantation are becoming more and more chemotherapy-based. But nonetheless, access to a TBI facility is a necessity in a pediatrics unit.

7. What means of immobilization techniques are used for children?

Immobilization is a fundamental step in delivering radiotherapy to children, compared to adults, because they cannot remain still or understand the need to do so.

"Immobilization" is done in three ways:

7.1. Charm by the medical, paramedical and technical staff. Collaboration with the mother: usually, in all departments, the rule is that the parents or the patient's family are not allowed standing at the machine control panel while the treatments are being performed. Departments violate that rule if they think that it will help the child calm down: the mother sits at the intercom (intercom system communicating with the treatment room) and reads the child a story while the treatment is taking place. This is very helpful for tranquilizing the young patient (Drs. Palta and Ziongas).

7.2. Sedation. Satisfactory immobilization can be achieved for children without using very heavy, but mild sedative agents, to a level that does not require an anesthetist to be in attendance. Doctors do not find a need for general anesthesia during radiation treatment of children, but for safety reasons the department needs the flexibility to start a general anesthesia case on 24-hours notice. This is absolutely essential (Dr. Macliss). In the majority of centers, only two or three children have to be sedated on average per day among 15-20 to be treated.

A general rule is: For children younger than the age of one, generally they can simply be held in place by immobilization, or maybe just be given a mild sedative. For children between the ages of about one and four, they require daily anesthesia, as they cannot simply be held in place. They do not have intellectual maturity. And, finally, for children over the age of four, most of them have the intellectual maturity to hold still while we work with them.

The nurses need to be very keyed into this factor and they often have to spend a lot of time with the families suggesting ways that the parents can help the children learn to hold still for the treatment.

In these general comments, some specialists added the specific experience of their department: Dr. Kun - St. Jude's rarely requires sedation for children over the age of three. Very often he is able to work without sedation for kids who do not require complex treatments down to the age of two. He uses sedation and infrequently requires general anesthesia largely for children with neuroblastoma or specific types of brain tumors that tend to sedate rather poorly.

7.3. Immobilization devices. Ideally, the immobilization device must be custom-tailored, and not a standard one. The purpose is to have the patient in the most comfortable position for precision, and not to restrain or freeze them. So, as a guide the following rules can be applied:

7.3.1. Incorporate specific modifications to the treatment couch (for supine cranio-spinal irradiation for younger children or those who require sedation).

7.3.2. Creation of a pleasant and joyful environment during therapy.

7.3.3. Use of normal, simple immobilizing devices like straps, adhesive tape bandages, plaster bandages.

7.3.4. Alpha cradle capabilities which are used for several techniques.

7.3.5. Customized cast that can be used with the patient preferably in a prone position for cranial-spinal irradiation. These special cut-out supports should gently surround the patient's face with foam while allowing plenty of air for the patient to comfortably breathe.

7.3.6. Include devices to distract or interest children.

7.3.7. It is very important to have a good machine shop support (or at least good accessibility) and a good machinist, to create special accessories or holding devices to make the patient comfortable.

The time spent for localization, simulation and first treatment may be as much as a factor of 3 to 4 comparing to an adult setup, because most of the time is spent in reassuring the patients that everything is going to be fine, it is not like getting an injection or anything like that, they do not feel any pain and even if they are alone in the room for a few minutes, doctors and parents can see them from the outside. This way, once the children are assured that nobody is going to harm them, they are the best patients (Dr. Palta). They do not move at all. So you don't really have to freeze them using fancy immobilizations.

To conclude this subject, we note that Dr. Macliss emphasized: "When I spent time at the Cambridge MRC Radiotherapy Unit recently, almost every case, and especially every pediatric case, had a special cast made for every patient. They wouldn't consider doing a pediatric case without it in England."

8. Which recent technological developments in Radiotherapy (i.e. 3-D Imaging, Conformal Therapy, Multileaf Collimators etc.) do you think would be valuable for the treatment of children and why?

At present, the use of recent technological developments even in the most developed pediatric radiotherapy departments is very limited. Some specialists believe that, for example in cases for brain tumors, treatment fields are fairly large and they have to use rather simple conformal techniques. So, advanced technologies will only rarely be necessary in children, whereas they are fully developed in the adult. On the other hand, as Dr. Macliss stresses, "potentially, over the next 10 years most of the emphasis in advances in pediatric radiotherapy is going to come from treating less normal tissue, because that is where complications appear."

Furthermore, several opinions have been expressed on some other techniques:

8.1. Proton therapy. As Dr. Jenkins stated, "there is very little indication for proton therapy in childhood. In the last ten years we didn't refer any patient to a proton therapy facility".

8.2. Stereotactic radiosurgery. According to Dr. Macliss, stereotactic radiosurgery is unproven in terms of increased efficacy compared to conventional radiotherapy. It is obviously superior in terms of decreasing the amount of normal tissue that it treats, and for that reason it could have a very important place in the treatment of children. Dr. Jenkins expressed the opinion that there will be exploration of stereotactic radiosurgery in the future, particularly for very small recurrent brain tumors. But the majority of specialists agree that there are not many indications in childhood for high dose and very small volume irradiation.

For the small number of children which need stereotactic irradiation (according to Dr. Jenkins, 1-2 cases/year) it would not be justifiable to install such a facility in a children's radiotherapy department. So, radiosurgery should be considered advisable, and it is better to refer the child to a center that has substantial experience with this method rather than treating the occasional child. But, the thing to be careful about is patient transportation for radiosurgery and anesthesia support is a key issue as well.

On the other hand, according to Dr. Palta, it is very easy to install a radiosurgery facility in a fully-equipped department with little extra cost.

8.3. Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI). CT and MRI are regarded essential for treatment planning. For pediatric patients, MRI and CT correlation is routinely used in treatment planning (Dr. Palta, St. Jude's Children Hosp.).

For the most cost effective use of resources, there is no need, as the number of the patients is not high, to have a CT scanner or a CT-Simulator device and an MRI facility at the radiation department, if three conditions are met: The institution owns a CT scanner and the department has a dedicated time on it for its own patients, they have access to a MRI facility, and own a simulator in the department.

8.4. Multileaf collimators. A number of specialists believe that the use of handmade special beam shaping devices, such as cerrobend trays, is superior to multileaf collimators in providing conformal therapy. The utilization of multileaf collimators on the machine would be primarily for conformal therapy, or dynamic therapy, and not for field shaping. Dr. Palta says that he prefers blocks for pediatric patients because blocks give less of penumbra. Multileaf collimators, depending on whether they are double focused or single focused multileaf, have a penumbra which is greater than that of a conventional block. The edges are zigzagged rather than fine, and for small pediatric patients, sometimes a uniform block shape is very important, because it might have a critical structure right next to the target. For a pediatric patient, a multileaf collimator would only be useful in dynamic therapy when the aim is to conform and minimize the area to be irradiated (Dr. Palta).

8.5. Hyperthermia. Doctors are not in favor of hyperthermia at this point for any known indication in pediatrics. For them

this is an experimental area where it is as yet unclear whether there are going to be any particular advantages in children. As Dr. D'Angio stated, "the role of hyperthermia remains to be defined in cancer in general and I know of no large experience obtained in children".

CONCLUSIONS

This study provides an overview of the necessities for establishing a radiation oncology unit dedicated to the treatment of children with malignancies, as seen from the point of view of radiation oncologists active on clinical research in this field. Because of this academic bias, the opinions presented here do not necessarily reflect an accurate picture of the current practice of treating children with cancer worldwide. In this sense, the value of this study as a document of evidence-based current clinical practice is limited. What it does confirm, is the important role that Radiation Oncologists play in the management of children with cancer.

The opinions expressed by this small group of experts can be summarized as follows:

1. The most important aspect of pediatric radiation oncology is staff dedicated to and knowledgeable of pediatric oncology.
2. The technology for radiation oncology that will improve our treatment results and diminish the late side-effects is clearly driven from the adult sphere, rather than the pediatric sphere. Anybody who is dedicated to pediatric radiation oncology must be bound, either academically or administratively, to an adult department of radiation oncology. The developments in treatment planning and treatment techniques are best based upon the far larger number of patients and the resources one would expect in a full-scale academic department.
3. Quality control of the treatment machines is more crucial, since the allowed tolerances are smaller.
4. It would be ideal to install a complete radiotherapy department with everything it entails in the average children's hospital. The reason that such an arrangement would be ideal is that all the facilities and personnel familiar with the management of children would be readily available. The next best solution is a radiation therapy facility installed at a general hospital. This way, the advantages of having the pediatric personnel very close is gained, while not sacrificing the economy and efficiency gained by using the services of a complete radiation therapy department, needed for the much larger number of adult patients.

It is clear that the future will be challenging for Radiation Oncologists involved in the treatment of children with cancer. Despite the fundamental changes which have been taking place in the treatment of this group of patients, all indications suggest that radiotherapy will maintain its role in curative children cancer treatment and Radiation Oncologists will find an important role, actively participating in the design and execution of appropriate clinical trials.

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Nutrition in cancer patients

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ABSTRACT

Nutritional disorders in cancer patients are common and have important prognostic value. Cachexia, an extremely debilitating nutritional disorder, is often present in advanced cancer patients. The development of cachexia involves functional, metabolic and mechanical causes. The location, histology and stage of cancer as well as type of therapy all impact on nutritional status. Physicians need to be aware that early detection and nutritional intervention are essential to minimize malnutrition, improve patient outcomes and lower health care costs.

Key words: cancer; cachexia; malnutrition; nutritional support; enteral nutrition; parenteral nutrition.

INTRODUCTION

Cancer patients suffer from the highest rate of malnutrition among hospitalized patients. A more than 10% weight loss is observed in 45% of cancer patients (1). The presence of malnutrition in cancer patients ranges from 9% in breast cancer to 80% in oesophageal cancer (2, 3); it is more common in children and the elderly (4). Weight loss is the primary presenting symptom in newly-diagnosed cancer (5). Nutritional status is highly correlated with the cancer patients' quality of life, response to treatment (6), morbidity and mortality (7). Nutritional support for cancer patients is essential to promote optimal healing and therapeutic outcome (8, 9).

Cancer cachexia, an extreme form of malnutrition, is a clinical syndrome characterized by a constellation of symptoms including progressive body-weight loss, anorexia and reduced food intake, easy satiety, muscle-mass loss, muscle weakness and various biochemical disorders (10, 11).

PATHOPHYSIOLOGY

Cancer cachexia differs from malnutrition or starvation due to multiple metabolic aberrations (12) (Table 1) associated with it. A negative-energy balance results from anorexia, and increased energy consumption, which is usually mild (100 to 300 kcal/day), but can cause body-fat loss of 0.5-1 kg/month and muscle-mass loss of 1-2.3 kg/month (13).

Theories explaining metabolic abnormalities in cancer patients include an exaggerated or increased activity of the Cori cycle, a channeling of carbohydrate intermediates towards lipogenetic pathways, and increased protein turnover.

Although anorexia is a primary factor in the development of cachexia, it does not completely

Table 1.
Metabolic abnormalities in cancer patients

Carbohydrates
Increased gluconeogenesis from amino acid, lactate and glycerol
Increased glucose disappearance and recycling
Insulin resistance
Lipids
Increased lipolysis
Increased glycerol and fatty acid turnover
Lipid oxidation non-inhibited by glucose
Decreased lipogenesis
Decreased lipoprotein lipase activity
Non-constant increase in plasma level of NEFA
Non-constant increase in lipid plasma levels
Protein metabolism
Increased muscle protein catabolism
Increased whole body protein turnover
Increased liver protein synthesis
Increased muscle protein synthesis

Table 2.
Cytokine-mediated effects on protein, carbohydrate and lipid metabolism

Cytokine	Protein	Carbohydrates	Lipids
TNF	↑ muscle proteolysis ↑ protein oxydation ↑ hepatic protein synthesis	↑ glycolysis ↓ glycogen synthesis ↑ gluconeogenesis ↑ glucose clearance ↑ lactate production	↓ lipogenesis
IL-1	↑ hepatic protein synthesis	↑ gluconeogenesis ↑ glucose clearance	↑ lipolysis ↓ LPL synthesis ↑ Fatty acid synthesis
IL-6	↑ hepatic protein synthesis		↑ lipolysis ↑ Fatty acid synthesis
INF-γ			↓ lipogenesis ↑ lipolysis ↓ LPL activity

explain it. The provision of high calories by technical means does not necessarily prevent the progression of cachexia. Other possible factors involved are increased energy consumption by tumor (10), increased energy consumption during rest, REE (Rest Energy Expenditure) (14) and disorders of metabolism.

Cancer is associated with metabolic disorders of proteins, carbohydrates and lipids (Table 1). Cytokines play a key role and have been described as moderators of many metabolic disorders resembling cancer (Table 2) (13). Moreover, lipid mobilization factor (LMF) and protein mobilization factor (PMF) have been implicated in the catabolic process of cancer cachexia.

The cancer itself can also cause metabolic disorders contributing to cachexia. Tumors can be "nitrate traps", causing decreases in protein mass and other disorders of protein metabolism (15). Protein synthesis, primarily hepatic, is increased, while muscular protein synthesis is decreased. In contrast, in starvation states both hepatic and muscular protein production are decreased.

Carbohydrate metabolism may also be altered in cancer patients. An increase in production of glucose in the liver (gluconeogenesis) often occurs. This could result from multiple factors, such as an increased supply of gluconeogenesis-enhancing elements (alanin, lactic acid, glucerol), a decrease in the consumption of glucose by the skeletal muscles and an increase of glucose consumption by the tumor, with parallel accompanying increases of lactic acid production. These metabolic disorders are similar to those observed in patients with diabetes mellitus type II and stress-response states (16). Such physiological changes are due to increased resistance of insulin and, to a lesser degree, to a reduced insulin response to variations in glucose levels (17). The cancer lesions themselves, and not the malnutrition, are responsible for the increased insulin resistance. This is demonstrated by the increased effect of insulin after radical excision of cancers (18).

Lipid metabolism disorders in patients with cancer also occur. Lipid mobilization and the oxidation of free fatty acids increases and the removal of lipids from plasm is reduced. Tumor substances increase lipolysis and the release of free fatty acids and limit fat synthesis (19). These disorders are not inhibited by the administration of glucose (20).

Cancer patients present nutritional problems which are attributed to the lesion itself, to the antineoplastic therapy and to the psychological reaction of the patient to the cancer diagnosis. The location, stage of cancer and the histological type of the tumor are all associated with malnutrition. On the other hand, tumor size is not associated with cachexia (21) or weight loss. Tumors weighing less than 0.01% of total body weight can result in cachexia.

Cachexia can be caused by functional and/or mechanical problems. In the early stages of cancer, weight loss is associated with limited food intake, increased nutritional needs, malabsorption of substances and their rapid passage through the gastrointestinal (GI) tract. In advanced stages, malnutrition is caused by alterations in metabolism (22). Although, cancer patients with cachexia consume 800 calories less per day than patients without cachexia (23), the reduction in calorie intake does not always result in a decrease in body weight. Even though these patients consume less energy, they catabolize their muscle tissue,

sparing lipid tissue, in order to produce needed energy (24).

Mechanical causes of malnutrition include the obstruction of the GI tract by the tumor and compressive phenomena in the abdomen resulting in the sense of filling and reduced food intake.

The immune system substances, cytokines, also affect metabolism and cancer malnutrition, although to what degree is not completely understood. Cytokines, including tumor necrosis factor (TNF) and interleukins, produced by the tumor and by healthy tissue, contribute to both anorexia and alterations in the metabolism of carbohydrates, proteins and fats (6). Tumor necrosing factor limits the action of the lipoprotein-enzyme lipase causing an increase in fat metabolism. Interleukin-1, interleukin-6 and TNF affect protein metabolism and are involved in the reduction of muscle mass (25, 26).

Surgical intervention can directly and indirectly affect the nutritional state of the cancer patients. The location of the surgical trauma can cause additional nutrition problems. Surgical procedures located in the head and neck can cause dysphagia (27). Surgery in the stomach, pancreas or the intestine can cause malabsorption, a sense of filling and meteorism (28).

Aggressive antineoplastic therapy also worsens the nutritional state of cancer patient, and the combination of aggressive antineoplastic therapy and malnutrition enhance toxicity (29) and mortality (30).

Chemotherapy frequently causes anorexia, nausea and vomiting, stomatitis, dry mouth, changes in the sense of taste, diarrhea, enteritis and/or constipation. These adverse reactions result in reduced food intake and a deterioration in nutritional status (24, 28). In addition, chemotherapy can change the intestinal mucosa, affecting the speed of passage of nutrients and their absorption by the intestinal villi (24).

Radiation therapy can also impact nutritional status, depending on the dose, location and frequency of radiation and the co-application of chemotherapy (8, 24). Up to 90% of the patients receiving radiation to the head, neck and abdomen experience weight loss (31). Radiation to the chest causes eosophagitis and dysphagia (32).

Immunotherapy results in reduced appetite and intense fatigue.

Finally, the diagnosis of cancer frequently triggers a psychological state of fear, anxiety, depression, anger, anorexia (33, 34). As a result, reduced food intake, indigestion and anorexia are often observed in cancer patients (35, 22).

NUTRITION

Malnutrition is a common problem in patients with cancer (36). Estimated prevalence rates of malnutrition vary according to tumor site, stage of disease, type of treatments and the methods used to identify the condition. They range from 9% in urological cancer, 46% in lung cancer, and up to 85% in pancreatic cancer patients.

Cancer cachexia is associated with metabolic abnormalities, anorexia, early satiety and reduced food intake, muscle weakness, oedema, fatigue, impaired immune function, changes in taste and reduced reflexes and difficulties in concentration (37).

The aim of nutritional support is the prevention or reversal of nutritional decline and progression to cachexia (38). Nutritional therapy can be used as an adjuvant treatment during anticancer therapy or as long-term nutritional supplement to patients unable to maintain adequate nutritional intake. Strategies for nutritional support include dietary counseling, oral nutritional supplements, enteral tube feeding and parenteral tube feeding (6).

NUTRITIONAL REQUIREMENTS

Assessment of nutritional requirements of patients with cancer is usually carried out by a dietician following referral for nutritional advice. The energy requirements of patients with cancer depend on the degree of malnutrition and metabolic stress, on energy losses and the level of physical activity. Metabolic requirements of patients with cancer may be increased, decreased or normal, depending on the status of the individual. Individual nutritional requirements can be calculated using formulas, such as the Harris Benedict or Schofield equations, with the addition of a stress factor, depending on weight change and/or disease progress.

Alterations in protein metabolism are common in cancer (39). These include increases in whole-body protein turnover, increased protein synthesis and catabolism, as well as an increase in skeletal muscle breakdown and a decrease in its synthesis, all of which result in muscle wasting. In clinical practice, the protein requirements of patients with cancer are often determined by adjusting the estimated requirements of healthy individuals, to account for the stress induced by the disease and treatment. Estimated protein requirements range from 1.2 to 2.0 g/kg/day, depending on the state of malnutrition and metabolic stress (37).

Patients with cancer may be at risk of developing micronutrient deficiency as a result of reduced intake and increased losses of micronutrients. Nutrient deficits have specific adverse effects on immune competence, including reduced lymphocyte response to mitogens, altered cell-mediated immunity, phagocytic dysfunction, impaired cytotoxic T cell activity and others (40). Adequate supply of micronutrients is essential to optimal cancer treatment.

DIETARY INTERVENTIONS

A nutritional support plan for patients with cancer should be tailored to individual nutritional needs, nutritional status, dietary restrictions, tolerance and feasibility, gastrointestinal (GI) function, medical condition and the current and expected side effects of treatment. Early nutritional intervention is

essential for improving patient outcome, even for those not currently malnourished (41). In addition, early nutritional intervention considerably reduces healthcare costs due to shorter hospital stays (42).

NUTRITIONAL SUPPORT

There are various intervention strategies to support patients with declining nutritional status. The choice of strategy depends on the level of malnutrition and the resources available, ranging from dietary counseling in the preventative, early stages of diagnosis to complete enteral nutritional support in patients that are unable to meet their nutrient requirements orally. In current clinical practice, it is uncommon to advocate parenteral nutritional support, although there may be rare instances when it is indicated for patients with cancer.

Studies suggest an association between poor nutritional parameters and worse overall morbidity and quality of life in patients with cancer (43).

Dietary counseling aimed at improving food intake of patients with cancer via normal foods and beverages is usually the first step in the provision of nutritional support, before patients become malnourished (44).

Oral supplementation

Oral nutritional supplements are effective when patients are unable to meet requirements with normal foods alone, despite dietary counseling (45). Oral supplementation is the simplest, most natural and least invasive method of increasing nutrient intake in all patients. Suggested benefits of oral supplementation include increased appetite and weight gain, decreased GI toxicity and improved performance status. In addition, oral supplementation results in increased immune response and an increase in energy and protein intake (46). High-fibre intake has other positive benefits including improved absorption of nutrients, gut transit time, stool characteristics, and possibly immune function (47).

Novel approaches

Eicosapentaenoic acid (EPA) is a novel compound included in supplement feeds. It is an essential long-chain polyunsaturated fatty acid of the n-3 fatty acid series. Studies suggest that EPA attenuates cancer-related wasting, improves immune function, halts or reverses weight loss, modulates the acute-phase response and prolongs survival (48). In studies of patients with pancreatic cancer cachexia, the use of EPA reduced serum levels of C-reactive protein and interleukin (IL-6) production by peripheral blood mononuclear cells (PBMCs) (49).

In a non-randomized study, EPA supplementation resulted in weight loss stabilization in patients with pancreatic cancer. In addition, increases in weight, dietary intake, appetite, and performance status were observed (50). In randomized studies in patients with cancer, EPA was associated with an increase in survival and performance status, and a reduction in complications (51). In addition, EPA-enriched feeding was associated with a decrease in GI complications and infections and improvements in renal and liver function (52).

Antioxidants

Antioxidants may enhance the anticancer effects of chemotherapy by detoxifying reactive oxygen (53). For example, vitamin E was shown to prevent and treat chemotherapy-induced mucositis (54), while vitamin C reduced bleomycin-induced chromosomal damage in lymphocytes (55).

Enteral nutrition

Enteral-tube feeding is indicated for patients who are unable to meet their nutritional needs by oral intake through diet or sip feeds alone. This may be due to an inability to eat resulting from dysphagia, upper or lower GI obstruction, or central nervous system pathology. Enteral-tube feeding is also indicated in cases where nutritional needs can not be met due to impaired digestion or absorption (37).

Randomized trials show that clinical outcome is improved in severely malnourished patients with cancer who receive enteral nutrition in the early post-operative period. Early post-operative tube feeding reduces complications (56), improves nitrogen balance, reduces protein breakdown, increases immune response (57), and reduces infections and length of hospital stay (58). Enteral nutrition also reduces toxicity from chemotherapy in the GI system, improves response to chemotherapy and increases immune response. Moreover, it improves the quality of life in malnourished patients with head and neck cancer during the preoperative period (59). Enteral nutritional support (oral nutritional supplement or enteral tube feed) in patients with cancer (36) significantly reduces duration of hospital stay, as well as infectious and non- infectious complications compared with parenteral nutrition. Enteral nutrition results in better quality of life and decreased health care costs (36).

Parenteral nutrition

Parenteral nutrition is rarely indicated in patients with cancer due to the associated high risk of sepsis and increased hospital stay (36). However, in cases where enteral nutrition support is not possible, parenteral nutrition is indicated. Home parenteral nutrition results in physical, social and cost benefits for cancer patients and their families (60).

There are no specific, globally-accepted nutritional guidelines available for cancer patients. However, general guidelines for the nutritional support of patients with cancer exist (61, 62).

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Case reports of two patients with metastatic pancreatic cancer and long-term survival (over 39 months) and literature review

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ABSTRACT

Pancreatic cancer remains one of the most challenging neoplasms to treat and one of the most fatal neoplastic diseases. Although it is associated with a dismal prognosis, we describe two rare cases of pancreatic cancer with long-term survival: the first one concerns a 54-year old woman and the second a 61-year old man. They are both treated for ductal adenocarcinoma of the pancreas with medium and poor differentiation. Both of them achieved a long-term survival (66 and 39 months, respectively), treated by modern chemotherapy.

Key words: ductal adenocarcinoma; pancreatic cancer; docetaxel; erlotinib; gemcitabine; bevacizumab.

INTRODUCTION

Pancreatic cancer remains the fourth leading cause of death due to cancer in both sexes. The overall 1-year survival rate is about 23% and the overall 5-year survival rate is less than 4%, with an overall median survival of 3-5 months (1). Long-term survivors are actually uncommon, due to the fact that the majority of these patients are diagnosed while being in an advanced, unresectable and metastatic stage. Although surgical resection of the tumor and selected surrounding tissues is the most effective therapeutic strategy, only 10-15% of the patients present with localized tumor without metastasis. The rest of them have considerably advanced disease at the time of diagnosis. We describe a case of a 54-year old woman that survived for 66 months (5.5 years) and another one of a 61-year old man who still survives for more than 39 months (over 3 years) after diagnosis of pancreatic adenocarcinoma, respectively. Both patients were part of a larger study, the results of which will be published shortly. Our clinic is responsible for the treatment of more than 80 patients with pancreatic cancer annually (most of them with dismal prognosis), making the report of such cases with extended survival very rare.

CASE 1

The first case pertains to a 54-year old woman who was operated in August 2004 for pancreatic cancer. She underwent a partial pancreatectomy as, due to tumor invasion, the surgeon could not perform a Whipple operation. Histological examination revealed a medium differentiated ductal adenocarcinoma in the pancreas. The tumor had partially infiltrated the ampulla of Vater and the peripancreatic fat. Four of the fourteen lymph nodes that were resected, were involved ($T_3N_{1b}M_X$ - stage III). Starting in October 2004, she followed a chemotherapeutic treatment that included Docetaxel 60 mg/m^2 at day 1 and Gemcitabine 1000 mg/m^2 at days 1, 8 for 6 cycles (each cycle was repeated every 21 days). After the third cycle, the doses were reduced because of increased liver function tests (SGOT=174 IU/l, SGPT=212 IU/l, LDH=513 IU/l, γGT=94 IU/l). The initial levels of the liver function tests (in December 2004) were SGOT=35 IU/l, SGPT=59 IU/l, LDH=282 IU/l, γGT=36 IU/l. Evaluation after the fourth cycle with computed tomography (CT) (February 2005) showed stable disease (SD) but the CEA and CA 19-9 serum markers were elevated. At the end of the sixth cycle, the patient stopped chemotherapy due to the fact that the CT, the total body positron emission tomography (PET) scan and the ultrasound (US) examination were negative for disease progression while the serum markers values returned to normal (CEA=2.4 IU/l, CA 19-9=28 IU/l). For the following two years (March 2005 - June 2007) the patient remained without any

treatment, reflecting her excellent response to the Docetaxel/Gemcitabine regimen and due to the behavior of the disease, while being under oncological evaluation. During this period, the imaging studies did not show any recurrence of the disease.

Two years later, in May 2007, the PET/CT scan revealed a small nodular shadow located at the posterior surface of the lower left pulmonary field, presumed to be either inflammatory or neoplastic in origin. For this reason, a wedge-shaped resection was performed. The histopathological report revealed metastasis from the pancreatic cancer with a diameter of 0.6 cm. In addition to this, Magnetic Resonance Imaging (MRI) examination of the upper abdomen showed relapse of the disease in the body of pancreas with a maximum diameter of 2.2 cm. Thus, a second chemotherapeutic treatment with Docetaxel 60 mg/m^2 (day 1 and day 15), Gemcitabine 1500 mg/m^2 (day 1 and day 15) and Erlotinib 100 mg per day was administered from June 2007 for 4 cycles every 3 weeks. Liver function tests and serum markers continued being elevated, but the total body CT scan on October 2007 revealed a small amount of pulmonary fluid and a reduction of the neoplastic mass size. The results were considered as mixed. In December 2007, she continued with single-agent treatment with Gemcitabine 1500 mg/m^2 for 2 cycles every 3 weeks. In February 2008, third-line chemotherapy was carried out using Docetaxel 70 mg/m^2 (day 1), Gemcitabine 1800 mg/m^2 (day 1) and Erlotinib 100 mg daily for 3 cycles every 3 weeks, due to an increase of the serum tumor marker levels (CEA=2.8 IU/l, CA 19-9=180.5 IU/l). We chose to continue the administration of Docetaxel, as it was the only approved treatment and due to its synergistic effect. Owing to a reduction in the size of the primary neoplastic lesion, the tumor become resectable, so the same surgeon performed a Whipple procedure (by resecting the remaining pancreatic tissue) on May 2008. After the operation, both the upper abdomen MRI and lung CT were negative for residual disease, with the patient continuing her chemotherapeutic program. A pulmonary CT, four months later, revealed a mild increase of the paracardial nodular lesion located at the left upper lobe and the chemotherapeutic regimen changed immediately. For this reason, the patient received Oxaliplatin 90 mg/m^2 (day 1), Gemcitabine 1800 mg/m^2 (day 1), Bevacizumab 7.5 mg/kg (day 1) and Erlotinib 100 mg daily from September 2008 until June 2009 (13 cycles, every 3 weeks). In the seventh cycle, Erlotinib was replaced with Capecitabine 2 g/m^2 daily for 14 days after each cycle, due to the serum markers increase.

In April 2009, the total body PET/CT scan showed a new lesion at the posterior arrow of the lower left rib. Also, MRI examination of the upper abdomen revealed a new metastatic site at the anterior lower pleura. Additionally, the whole body bone scan showed secondary osteolytic lesions on the seventh and eighth left rib for which she received radiotherapy. This relapse led us to use a new chemotherapeutic scheme. The patient was treated with Irinotecan 90 mg/m^2 (day 1), Bevacizumab 7.5 mg/kg (day 1), Gemcitabine 1800 mg/m^2 (day 1), Capecitabine 2 g/m^2 daily for 14 days after each cycle, Zolendronic acid 4 mg, Ibandronic acid 150 mg/day and Erlotinib 100 mg/day. After the completion of 6 cycles (that unfortunately were not every 21 days but sometimes more than 30 days apart as the patient complained of increasing fatigue and inconvenient travel arrangements -she had to make a long journey from the island she lived to our clinic), the patient denied any further treatment. She died, due to disease progression, in April 2010, approximately 3 months after her last treatment and 66 months after diagnosis of pancreatic adenocarcinoma.

CASE 2

The second case pertains to a 61-year old man who was diagnosed with a mass of the pancreas, after a Magnetic Resonance Cholangiopancreatography (MRCP) examination revealed a tumor between the head and the notch of pancreas, which constricted the main pancreatic duct and, partially, the portal vein. Five days later, an Endoscopic Retrograde Cholangiopancreatography (ERCP) was carried out during which a sphincterotomy was performed and a metallic stent was placed. The patient denied biopsies and so we started a chemotherapeutic treatment with Docetaxel 60 mg/m^2 at day 1 and Gemcitabine 1200 mg/m^2 at days 1, 8 for 13 cycles every 3 weeks, upon which the patient showed SD and no major toxicities. In April 2007, we started the second line of chemotherapy with Erlotinib 100 mg daily and increased the dose of Gemcitabine to 1500 mg/m^2 every 3 weeks, due to an increase in serum markers (CEA=7.29 UI/l, CA 19-9=1611.60 IU/l). This dose escalation was chosen not only because the chemotherapeutic scheme was well-tolerated by the patient but also so as to overcome possible drug resistance. A gradual reduction of the serum markers was observed but the liver function tests remained elevated (SGOT=73 UI/l, SGPT=65 UI/l, LDH=470 UI/l, ALP=342 UI/l, γGT=550 UI/l). He also developed a cervical rash after the third cycle, which was attributed to Erlotinib. In June 2007, the total body CT scan showed stable disease but the CA 19-9 serum marker increased rapidly and reached 2219.42 IU/l. He was in good performance status and did not feel any pain.

In August 2007, while the aforementioned biochemical parameters continued being elevated, the abdomen CT revealed some low-density lesions, with a maximum diameter of 2 cm, in part VII of the liver. The new finding led us to the gradual increase of Docetaxel to 80 mg/m^2. The CT restaging of the abdomen, in December 2007, showed disease progression (PD) as the hepatic lesions reached 4 cm in diameter and the titre of CA 19-9 was 978.67 IU/l. As a consequence, the patient started the third line of chemotherapy with Oxaliplatin 90 mg/m^2, Gemcitabine 1800 mg/m^2 both at day 1, 15 and Erlotinib 100 mg/day every 3 weeks for 6 cycles. One month later, the abdomen CT showed that both the mass of the pancreatic head and the hepatic lesions on the right lobe, which were assumed to be

secondary lesions with a maximum diameter of 5.5 cm, had grown. After three weeks, the patient was hospitalized for one month due to infection (positive blood cultures, neutropenic sepsis). His stay at the hospital delayed the next chemotherapeutic cycle, to which we added Capecitabine 2000 mg/day for 14 days after the first day of each cycle. In addition to this, the patient took Ocreotide due to many diarrheal episodes. In June 2008, MRI examination of the abdomen showed that the pancreas lesion had been reduced. Fortunately, this fact was accompanied by a reduction in the serum markers, with the patient being successfully operated on in September 2008 (Whipple operation), as the patient agreed with the surgeon who opted for resection based on the reduction of the pancreatic neoplastic lesion. During surgery, the surgeon also removed 2 smaller secondary lesions from the right liver lobe. Histological examination revealed a ductal adenocarcinoma, with a maximum diameter of 1.5 cm and medium-poor differentiation. The tumor had infiltrated small vessels and the duodenal loop fat. The histopathological report of the resected local lymph nodes revealed no metastatic lesions. Consequently, the tumor was classified as a $T_3N_0M_1$ cancer. The hepatic lesions on the right lobe had decreased in size, with a maximum diameter of 4.5 cm.

Postoperatively, the patient continued his treatment with a new chemotherapeutic regimen, which consisted of Gemcitabine 1800 mg/m^2 at day 1, Oxaliplatin 90 mg/m^2 at day 1 and Erlotinib 100 mg/day - stop for one day every 3 days, every 3 weeks for 9 cycles. In November 2008, the total body scan was negative for tumor recurrence and the serum marker rates had already started declining. After completion of 9 cycles (April 2009), we changed the medications and he started receiving Irinotecan 120 mg/m^2 (day 1), Gemcitabine 1800 mg/m^2 (day 1) and Erlotinib 100 mg daily - stop for 1 day every 6 days, biweekly for 5 cycles. In July 2009, the gradual increase of serum markers led to the addition of Capecitabine 3000 mg/day for 14 days after the first day of each cycle and he followed the new treatment for 4 cycles (every 15 days). Unfortunately, in September 2009 his disease relapsed as shown by the gradual increase of the serum markers (CEA and CA 19-9) and the appearance of secondary hepatic lesions in the upper abdomen MRI scan. For this reason, we replaced Irinotecan with Oxaliplatin. The patients remains in a very good PS but his serum markers continue to increase (CEA=11.07 IU/l, CA 19-9=636.16 IU/l). His last imaging study (March 2010) showed SD. The patient is still alive 39 months after the diagnosis of pancreatic adenocarcinoma, continuing his chemotherapy.

DISCUSSION

Pancreatic cancer, a malignant neoplasm with generally poor prognosis and extremely rare complete remission, is sometimes referred to as a "silent killer" because of its late presentation of non-specific symptoms, such as pain in the upper abdomen, jaundice, weakness, loss of appetite, nausea, vomiting, and weight loss. Several procedures may be performed by the physician in order to diagnose the disease including physical exam; laboratory tests; imaging studies (CT, transabdominal or endoscopic US, ERCP); and biopsy. In order to plan for the most appropriate treatment, the physician must determine the stage of the cancer based on tumor size and the presence or not of metastatic sites.

In our first case, the tumor was histologically classified as $T_3N_{1b}M_X$ (stage III) and in the second as $T_3N_0M_1$. In both cases, treatment with Gemcitabine is considered as the best available scheme for chemo- and radiochemotherapy, since the latter is acknowledged as a more effective radiosensitizer than Fluorouracil (5-FU) (2). However, because of the nature and prognosis of the pancreatic cancer, even such therapies do not reach the anticipated survival prolongation. Gemcitabine and 5-FU increase overall survival from 2-3 months when untreated to 6 and 5 months, respectively (2). Gemcitabine increases significantly the patient's quality of life and, from that point on, its combinations have been intensively scrutinized for increase of survival (1). Also, Gemcitabine confers additional advantages like pain reduction and improvement in performance status (3). A recently conducted meta-analysis using the majority of available randomized clinical trials (19 trials from 1996 to 2004) showed significant improvement in overall survival at 6 months and 1 year with Gemcitabine-based combination chemotherapy vs. Gemcitabine alone (4). Between the combination agents employed and Gemcitabine monotherapy with overall survival as the primary clinical endpoint, only the co-administration of Erlotinib significantly improved patient survival (5, 6).

Within this framework, the Gemcitabine/Erlotinib combination has gained approval from the FDA in 2005, as being able to increase survival by 0.33 months over Gemcitabine monotherapy (7). Out of all other second agents combined with Gemcitabine, the basis for Erlotinib effectiveness in pancreatic adenocarcinoma is that pancreatic cancers display high epidermal growth factor receptor (EGFR) expression levels and Erlotinib, as a specific EGFR inhibitor, diminishes its downstream stimulatory signaling during therapy (8, 9).

Docetaxel has a broad spectrum of antitumor activity and has been previously shown to present objective response rate of 20% with a median survival ranging from 212 to 442 days in patients with pancreatic cancer (10). Our group has previously estimated the accrual 1-year survival at 36.4% in patients with stage III and IV that had a histological confirmation of advanced pancreatic cancer (11). In addition to this, two other studies showed that Gemcitabine-based chemotherapy (combination of Gemcitabine with Docetaxel and/or Erlotinib) may increase pancreatic cancer patient survival to 5.3 and 7.89 months (12, 13). In our cases, we used the Gemcitabine/Erlotinib plus Docetaxel combination in order to stabilize the disease and increase the overall survival (66 and 39 months, respectively). The survival of our case reports differs a lot from the one previously reported by

Dragovich *et al.* (median overall survival of 12.5 months), and Iannitti *et al.* (median overall survival of 14 months) (14, 15). Despite the conflict and criticism of clinical trials that group stage III and IV patients together and the questions regarding the cost-effectiveness of the combination treatment (16, 17), our case reports show that overall survival is positively affected by the co-administration of Gemcitabine and Erlotinib with Docetaxel.

Platinum analogues in combination with fluoropyrimidine or with Gemcitabine represent another common schedule in clinical practice with data from single-centre or multicentric phase II studies (18). The safety and efficacy of chemotherapy (Gemcitabine plus Capecitabine) plus Erlotinib and off-label Bevacizumab in advanced pancreatic cancer because dual epidermal growth factor receptor/vascular endothelial growth factor blockade has a rational biologic basis in this malignancy is also under scrutiny (19).

The authors' intention is not only to present two rare cases of patients with pancreatic cancer that exhibited extended survival (in contrast to most patients that have a dismal prognosis and only a few months of survival) but also to remind physicians of the need for individualized approach to patients. The presentation of these cases should not be used as a rough guideline when treating patients with pancreatic cancer in an oncology ward. Instead, the treating oncologist should tailor the chemotherapeutic treatment according to the stage of the disease and the patient's response (or not) to a specific regimen, so as to be prepared to make dosage adjustments and switch from 1st to 2nd and to 3rd line treatment if required.

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Caries treatment in head and neck radiotherapy and chemotherapy patient: a case report

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ABSTRACT

Therapeutic doses of radiation and chemotherapy induce long-term damage to the salivary glands, connective tissues, vasculature, dental hard tissues and jawbone healing potential. Mucositis, xerostomia, radiation caries, taste loss, trismus, osteonecrosis and osteoradionecrosis are the most common oral complications from cancer therapy. Oral health management plays an important role in preventing such complications. The goal of dental management is both to eliminate oral disease and prevent, minimize or treat the complications resulting from cancer treatment and at the same time, maintain dental health and function. The dental specialist is expected to know the possible cancer therapy adverse effects and, thus, proceed in taking therapeutic actions that do not risk the onset of undesirable situations for the patient. In this case report, the clinical procedure of dental management of one oncology patient, after chemotherapy and radiotherapy in the head and neck region, is presented.

Key words: oncology patient; radiotherapy; chemotherapy; radiation caries; xerostomia.

INTRODUCTION

Despite the progress observed over the past few years in antineoplastic therapy, head and neck region chemotherapy and radiotherapy are accountable for the occurrence of complications in the mouth, the severity of which depends to a large extent on the patient's oral health.

In order to eliminate oral complications of cancer treatment as much as possible, the dentist's role is crucial in all phases of cancer therapy. Oral care should be considered as a contribution to the total patient care, while the dentist's active attendance in the oncology team can contribute both to the achievement of a therapeutic result and the improvement of the cancer patient's quality of life (1, 2).

Antineoplastic treatment complications are related either to the direct cytotoxic action of chemotherapeutic medicines, or indirectly to the immunodeficiency caused by them. Radiotherapy results in an alteration of saliva composition, xerostomia, mucositis, loss of taste, osteoradionecrosis and radiation caries, as it affects both hard and soft tissues at the same time (1, 3, 4).

The oral assessment constitutes an important aspect of patient preparation before chemo and radiotherapy and should take place two to four weeks before the beginning of treatment. Preventive dentistry and the subsequent treatment planning, aiming at the elimination of potential sources of infection, are of particular importance for the prevention of oral cavity complications. Consequently, the patient is monitored by a dental specialist throughout the cancer treatment, for the immediate alleviation of painful symptoms of hyposalivation and oral mucositis. Given the high risk of oral infections, prevention is of major importance, as a significantly lower incidence of severe oral mucositis at the end of radiotherapy was observed in patients with antifungal prophylaxis (20, 21). Subsequent to cancer therapy, patients should be on a follow-up and maintenance program, the frequency thereof being dictated by individual needs, taking into consideration that they should be closely evaluated for radiation caries, with particular emphasis on the maintenance of impeccable oral hygiene (1, 4, 5).

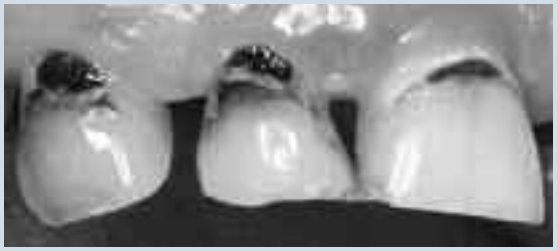
This case report presents caries treatment of an oncology patient, submitted to chemo and radiotherapy. The patient presented at the Athens University Dental School, requesting the re-establishment and stabilization of his oral health.

CASE PRESENTATION

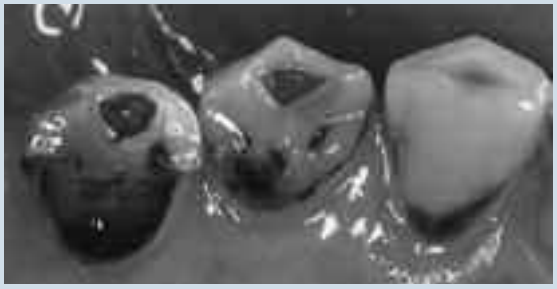
Medical history

A 54-year old male was referred to the Oper-

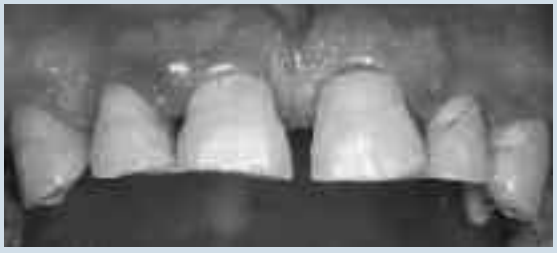
Picture 1.
The characteristic morphology of "radiation caries"



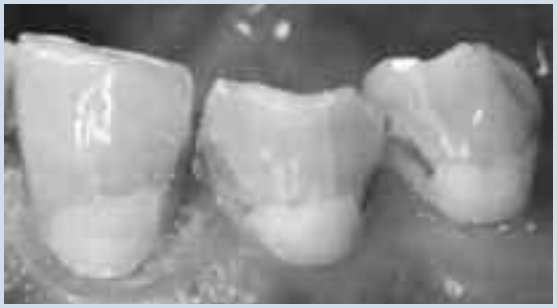
Picture 2.
Radiation caries extends circularly on the cervical areas of the teeth, affecting smooth surfaces and cusps



Picture 3.
Restorations of the carious lesions in the aesthetic zone with composite resin



Picture 4.
Provisional restorations with glass-ionomer cement



ative Dentistry postgraduate department clinic, from the Athens University Dental School Hospital Dentistry Clinic. In 2003, the patient was diagnosed with Hodgkin's Lymphoma (HL). The therapeutic scheme to which he was submitted consisted of three chemotherapy cycles with doxorubicin, bleomycin, vinblastine, dacarbazine and Waldeyer's ring and lymph node radiotherapy in the head and neck region, with a total radiation dose of 3000 cGy. The antineoplastic treatment was completed in March 2004. Since then, the illness is in complete recession and the patient is on a follow-up program every two years.

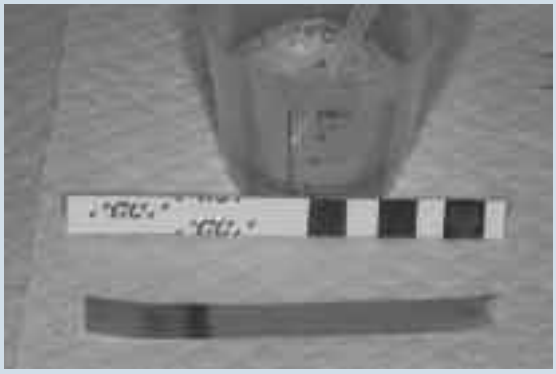
Treatment protocol

The patient presented for dental treatment 5 years after completion of the antineoplastic treatment. The information concerning his medical history as well as the present situation of his general health was provided in written form by his hematologist. From his dental history, the patient reported extractions of decayed teeth, before the beginning of chemo and radiotherapy; however, unfortunately, none of the essential preventive measures was taken for the maintenance of oral health and function.

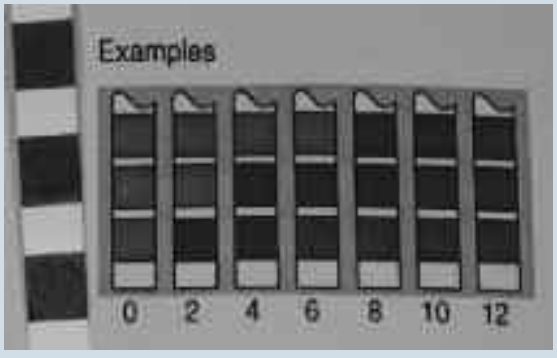
During the clinical examination, caries was detected and recorded on every tooth of the remaining dentition, with the characteristic morphology of radiation caries (pictures 1, 2). Radiation caries extended circularly on the cervical areas of the teeth, affecting smooth surfaces and cusps, including even mandibular anterior teeth, which is unexpected, given the fact that these areas are the most resistant to caries in non-irradiated populations (6). At the same time, changes in color and translucency were observed as brown and black discoloration of the entire tooth crowns, with increased wear of the incisal and occlusal surfaces. The acute response of the salivary gland tissue to radiotherapy was confirmed clinically by controlling the major and minor salivary glands secretive activity. Despite the fact that xerostomia is usually reversible below 4000 cGy, the patient reported a sense of dry mouth, which was also confirmed by objective signs. The flow rate of stimulated saliva was measured at 0.1 ml/min, with increased viscosity and reduced buffering capacity (pictures 5, 7). Saliva pH was measured using a special impregnated film (Saliva check buffer - GC) and was recorded as slightly acidic (picture 6). In order to confirm the patient's high caries risk, we examined caries activity, using a special commercial product (Clinpro Cario L - Pop (3M ESPE, Seefeld, Germany), capable of detecting the metabolic activity of caries-causing bacteria in the oral flora, on the basis of lactic acid formation rate. As expected, due to the presence of open cavities in most of the teeth, caries activity was found increased (picture 8). The patient was asked of any changes in his nutritional habits following completion of the treatment. Xerostomia, in combination with the deleterious effect of radiation in the aesthetic epithelium, cause a significant alteration of gustatory stimulants, which consequently result in a dietary shift towards soft, carbohydrate-rich food. Patients

Picture 5.
The flow rate of stimulated saliva was measured at 0.1 ml/min, with increased viscosity

Picture 6.
Saliva pH was measured with a special impregnated film and was recorded as slightly acidic



Picture 7.
Reduced buffering capacity of saliva



Picture 8.
Examination of caries activity through detection of the metabolic activity of caries-causing bacteria

usually consume large quantities of carbohydrates, so as to relieve themselves from the unpleasant symptoms of taste loss (6).

Subsequent to the recording of signs and symptoms, clinical and radiographic examination and occlusion analysis, a treatment planning was scheduled in collaboration with the postgraduate clinics of Periodontology, Prosthetics and Endodontology, with therapeutic goals that included control of the carious activity, restoration of carious lesions and patient aesthetic and functional oral rehabilitation. Taking into consideration the patient's difficulty to practice effective oral hygiene, because of the presence of large (in extent and number) carious lesions but also of the subsequent sensitivity, priority was given to the treatment and re-establishment of said damage. Carious lesions, although extensive, were restored with glass-ionomer cements, so as to achieve an oral equilibrium and stabilization, prior to proceeding with more permanent restorations. Accordingly, the patient was instructed in proper mechanical oral hygiene procedures. Glass-ionomer cements offer satisfactory anticariogenic action attributed not only to the release of fluoride but to their perfect sealing ability due to the chemical bond they form with dentine and enamel during the setting process (7). However, their poor mechanical properties, in combination with rapid degradation in acidic and xerostomic environments, impose restrictions on their use (8, 16). In order to achieve control and elimination of carious activity in this particular patient, emphasis was placed on the mechanic removal of dental plaque, with specific instructions and exercise of oral hygiene consisting of: brushing twice daily with 5000 ppm fluoride toothpaste, use of interdental means and 0.05% NaF fluoride solution once daily (13). Moreover, he was advised to alter his nutritional habits (sugar elimination diet and restriction in the consumption of sugar-containing refreshments and refined carbohydrates) and at the same time, the frequent use of water as saliva

substitute was recommended. Moisturizing oral gel was additionally subscribed (Biotene oral balance gel, GlaxoSmith-Kline, Middlesex, UK) for the alleviation of hyposalivation symptoms. Finally, an intensive fluoride program was implemented, including the application of 5% NaF fluoride varnish (Duraphat) during his recall examinations, which were scheduled every 4 months.

DISCUSSION

The most important oral repercussions of radiotherapy in the head and neck region consist of long-lasting, irreversible damage of salivary glands, dental hard tissues, oral mucosa and jaws, which have to be included in the radiotherapy portals. 84% of radiated patients present complications in the oral cavity, with hyposalivation (95%) and radiation caries (10%) being the most frequent (8, 19). The oncology patient should be considered and treated as a caries high-risk patient, with particular emphasis in the implementation of a preventive program before the onset of antineoplastic treatment, in order to eliminate potential sources of infection and, at the same time, prevent the occurrence of radiation caries (19).

Radiation caries is an indirect consequence of radiotherapy, since it is mainly caused by hyposalivation and alterations in saliva quality (1). Kielbassa *et al.* observed that the radiation directly affects the microhardness of dentin, which could probably explain the onset of caries at the dentin-enamel border. Gap formation across the enamel-dentinal junction eventually leads to microbial colonization (1). However, the primary factor, to which rampant caries is attributed, is xerostomia. Dietary changes, alterations in the ecology and microflora of the oral cavity, as well as immune system suppression, severely exacerbate the situation (9, 13). The observed shift in oral microflora towards cariogenic bacteria (increase in *Streptococcus mutans, Lactobacillus* and *Candida* spp.) combined with the reduced salivary flow and altered salivary composition result in an instant increase of caries risk (11, 14, 15).

Daily use of fluoride, effective and meticulous oral hygiene, restriction in the consumption of refined carbohydrates and sufficient hydration of the oral mucosa to treat the symptoms of xerostomia, constitute our weapons in the prevention of radiation caries (6). Indeed, xerostomia is an irreversible complication of radiotherapy for the majority of patients; thus, the threat of decay from radiation remains constantly present, which is why everyday use of fluorides and rigorous oral hygiene are of great importance.

In this particular case, the patient requested dental care long after the end of his cancer treatment, and as a consequence, treatment planning was limited to the therapy of oral complications that appeared after chemo and radiotherapy. Active participation on behalf of the dentist, throughout the oncology team treatment planning, is essential in every stage of the therapy. The first oncology patient dental evaluation must take place at least 14 days before the beginning of cancer therapy. The purpose of dental pretreatment evaluation is not only to prevent the onset of oral complications, but also to educate and inform patients on their important role in maintaining dental health. An interdisciplinary approach with a thorough dental examination before radiotherapy and a close monitoring thereafter are considered essential (18).

Patients should be on a follow-up and maintenance program with the frequency dictated by individual needs. The dentist's role is to eliminate the oral sequelae and help towards maximizing the inevitably reduced quality of life. Compliance with diet, oral hygiene and fluoride use needs to be closely monitored throughout the patient's life. Continued follow-up, as mentioned above, is also important to identify recurrence of caries, early osteonecrosis, or even local recurrence of the malignant disease in the oral cavity.

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On "Scientific Misconduct"

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Recently, a series of papers was withdrawn from high impact journals, like the *New England Journal of Medicine* (1) and the *Journal of Clinical Oncology* (2), as an author's data could not be reproduced by other investigators.

This incident caused significant upheaval in the oncologic community, followed by several publications in the lay press. More importantly, the withdrawn publications had lead to a series of trials which should not have taken place, as there was no basis for them.

Also recent was the final discrediting (and withdrawal of the related article in the *Lancet*) of the allegations regarding a link between autism and the MMR vaccine (3). These allegations were also based on inaccurate/false data, and caused many parents to avoid vaccinating their children, thus risking serious infections. The impact of scientific misconduct on society in general is serious and cannot be taken lightly.

A doctor involved in scientific misconduct is as dangerous as one whose practice of medicine is negligent.

As pointed out by the author of a recent article in the FCO (4), 'scientific misconduct' might lead to serious consequences -especially in medicine- and constitutes a serious violation of both the law and the Hippocratic Oath. Scientific misconduct can take several forms, such as plagiarism, self-plagiarism, fabrication, guest or gift authorship, ghostwriting, misappropriation of data and ideas of others and several other forms, described by the author in detail.

It is usually caused by purposeful cheating, aiming at promoting one's career or other rewards and it is dangerously unethical. What is alarming is that there is a «growing number of medical practitioners, students, researchers and teaching staff who think that cheating is not a big crime» (4). The problem of scientific misconduct is basically an ethical one. The fantastic progress in science, biology and technology that changed the world and us was not followed by a proportional progress in Ethics and Philosophy, both of which are lagging behind.

This discrepancy is expressed diachronically in the behavior patterns, characterized by a perpetual sway from the most glorious achievements to the most terrible monstrosities.

Ethics may be defined as the rules concerning good and evil but it is a manmade concept. As Shakespeare put it in Hamlet "there is nothing either good or bad but thinking makes it so". For practical reasons we would suggest a definition of Ethics as a set of rules concerning good and evil as accepted by a certain society, during a certain time period.

To deal with scientific misconduct, we need to emphasize ethics, a field that has been thus far dangerously neglected. In the absence of global ethics and a global philosophy, at the species' rather than the individual's level, the responsibility lies with the medical leaders (professors, medical directors, medical thinkers).

The medical leaders should create an intellectual environment in which intellectual satisfaction is drawn from the acquisition of new knowledge and the contribution to science, society and humanity.

The "publish or perish" slogan (4) is not only anti-intellectual but also antiscientific. One publishes when one has something to add to scientific knowledge, something useful to science and society in general.

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Key Words: 5-10, for indexing purposes.

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