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LETTERS TO THE EDITOR

Radiobiology and molecular oncology: how are they changing radiotherapy in clinical practice?

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To the Editor: At the 4th International Conference on Translational Research and Preclinical Strategies in Radiation Oncology (ICTR) held in Geneva, Switzerland, on March 11-13, 2009, more than 270 experiences from many parts of the world regarding innovation in radiotherapy approaches to cancer and radiation biology research were presented[1]. This confirmed the growing interest of radiation researchers in conducting preclinical studies at their centers and translating the results as soon as possible to clinical radiotherapy practice.

Recent papers have greatly enriched the current knowledge of radiation oncology, especially radiobiology and molecular oncology, and this has radically changed the oncology practice in radiation therapy in just a few years[1-17].

Radiotherapy is currently in the midst of new developments both in technology and radiobiology. High-tech improvements are refining the "ballistic" approach to delivering radiation to target volumes and the surrounding organ tissues by means of intensity-modulated radiation therapy or high-LET ionizing radiation as represented by protons and other hadrons[2,3]. The quality of images utilized in the control and monitoring of setup and tumor variations during treatment with image-guided radiation therapy devices is now at the same level as fine diagnostic radiology, and permits greater precision than was possible in the past[3]. However, the real revolution in radiotherapy derives from the stronger correlations between new radiobiological data and experimental results that are increasingly available and ready to be translated to clinical practice[4].

The long-term objective of the translational research program in radiation oncology is to improve the therapeutic window, minimizing the damage to normal tissue and increasing the efficacy of radiation in eradicating cancer. The selective inactivation of tumor cells in a solid mass is the most important finding related to the eradication of tumors by means of radiation without severely damaging healthy surrounding tissue. Recent experimental research has reported that tumors can be expected to recur after ionizing radiation treatment even if only one cancer stem cell survives[5]. Cancer stem cells are a specific subpopulation of cancer cells with high tumorigenic potential. In terms of clinical application, it should be investigated how cancer stem cells can be selectively destroyed, and whether they may respond differently to more selective radiotherapy and a more selective combined radio-pharmacological modality[6].

Radiation therapy can be customized to the individual patient and the effectiveness of radiation can be enchanced by targeted vector delivery and transcriptional regulation if a pathway in the tumor microenvironment is expressed, which will lead to selective eradication of the tumor. Studies are currently investigating, for example, the role of enzyme-inducible nitric oxide synthase (iNOS), which plays an important role in the proapoptotic and radiosensitizing effect on tumor cells. Gene therapy can thus permit, directly or indirectly, various degrees of radiosensitivity, with the endpoint of improving the effectiveness of radiation[7].

Biological heterogeneity of neoplastic cells is an important factor in the variable radiosensitivity within a tumor mass. Selective dose escalation to the more radioresistant parts of the lesion is considered feasible after the use of dose painting based on the increased availability of molecular imaging technologies such as PET, SPECT and MR imaging/spectroscopy[8]. High metabolism, high proliferation, and increased hypoxia now represent the targets for higher doses of radiation. New biological molecules fundamental in the tumor profile are being studied to reveal these and other features in detail. Hypoxia, for example, is known to be involved in the radioresistance of cancer. Hypoxia can be measured using 18FDG, 18F-labeled nitroimidazoles, and Cu ATSM, and has been demonstrated as a prognostic factor in many clinical studies[9]. "Theragnostic imaging" in radiotherapy is a new term used to describe the introduction of molecular images to define and more selectively treat each voxel of tumor volume with dose painting based on biological and functional characterization[10]. This type of approach is currently being routinely applied in many radiotherapy centers for various solid cancers, such as tumors of the head and neck area.

The correct determination of the single patient profile as well as single tumor behavior is the next challenge in radiation oncology. The routine personalization of treatment schedules will increasingly involve radiation oncology patients, as is currently the case with chemotherapy, by means of an individualized pharmacological approach where all predictive and prognostic factors are taken into account.

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To date, only dose-volume histograms have been available to predict toxicity for each patient before the initiation of radiation treatment. The violation of dose constraints of organs at risk may be predictive of the possibility of developing side effects. However, these data derive from the literature regarding radiation complications reported in large series. Therefore, there is an urgent need to define tools capable of addressing the real predictive value of the individual risk in patients undergoing radiation therapy. Theoretical models of tumor control probability (TCP) and normal tissue complication probability (NTCP) have been discussed in the radiotherapy community and applied in software developed to calculate them during planning. However, in-depth analyses of the best empirical TCP and NTCP models often differ significantly from idealized mathematical models[11].

Applied knowledge in genetics and epigenetics will be important to improve the efficacy and reducing the toxicity of curative radiation. Valdagni *et al.*[12] reported in 30 prostate cancer patients receiving 70 Gy that the predictive value of the sensitivity and resistance to rectal bleeding of 13 genes identified by the study is promising and should be tested in a larger data set.

Single nucleotide polymorphisms (SNPs) in many genes have been associated with a higher risk of late toxicity after radiation therapy. Some of these genes play a central role in induction or repair of DNA strand breaks by ionizing radiation[13,14]. ATM, XRCC1 and GSTP1 are examples of the most widely investigated genes in which SNPs could be correlated with various modalities of response to radiation, in terms of the risk of damage such as fibrosis. A tool to identify significant SNPs prior to treatment would allow radiologists to customize radiation treatment to the individual patient by modifying the total dose and dose per fraction based on the SNP profile.

In the field of radiosensitivity, preclinical models have investigated several biological agents with rapid translation to the clinical setting. Considering the frequently high level of EGF and/or VEGF receptor expression blocking, targeted therapies approach should lead to a dramatic improvement in radiotherapy results[15]. Many other novel therapeutic agents are being developed with the aim of introducing and modifying a specific pathway involved in cancer progression or in the response to treatments. Some of the new drugs have been used in monotherapy and their combined use should be promising, although additive toxicity to radiation can be expected[16,17].

Lastly, biology and high technology are strongly linked in the clinical implementation of nanoparticles. The integration of nanotechnology in cancer imaging and treatment will involve radiotherapy as well as chemotherapy[18]. The possibility to introduce radiation into the single cell by means of nanoparticles is one modality. The second is to more effectively enhance the effect of tumor cell elimination by radiation with the direct introduction, by means of nanovehicles, of therapeutic agents or radiosensitizers into the cancer cell, if possible at its most vulnerable point.

In conclusion, it is undeniable that the data reported here, along with other recent findings in radiobiology and molecular oncology, are changing both the knowledge and the point of view of oncologists in treating cancer with radiation. Despite these new changes, the radiation oncologist will probably remain more of a clinician than a biologist but a clear, direct relationship and a common language between researchers in preclinical oncology and operators in clinical practice is needed more than ever in order to move the new data quickly and effectively from laboratory to bedside.

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Palliative hepatic arterial infusion in renal cell carcinoma spreading to the liver: a retrospective analysis

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To the Editor: The liver is, in general, the most common site of metastatic disease. Resection is currently the only curative therapy, but the overwhelming majority of patients present with unresectable lesions and are treated by palliative chemotherapy that is administered systemically or regionally. Hepatic arterial infusion (HAI) of cytotoxic agents in patients with liver metastases has the advantage of a higher intratumoral drug concentration and less systemic toxicity[1]. In patients with colorectal cancer metastatic to the liver it was demonstrated in clinical trials that these theoretical advantages translate into superior response rates and quality of life[2]. It was, however, more difficult to demonstrate an improvement in survival. Consequently, the use of HAI in colorectal cancer metastatic to the liver is controversial. The role of HAI in patients with liver metastases of other primary tumors is even less clear.

Renal cell carcinoma (RCC) is a tumor with a peculiar biological behavior characterized by wide variations in its clinical course, including on the one hand spontaneous regression of metastases or an indolent course of metastatic disease, and on the other hand rapidly fatal metastases, paraneoplastic syndromes, or metastases at unusual sites. Metastatic involvement of the liver is common in RCC, but isolated liver metastases are relatively rare. RCC is characterized by resistance to virtually all cytotoxic agents[3]. Only biological agents, including the cytokines interleukin-2 and interferon-alfa, or targeted agents have reproducible activity in metastatic RCC. The experience with HAI of biological agents is very limited[4]. Here we present a retrospective analysis of a single-center study of patients with RCC liver metastases treated with HAI.

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A retrospective analysis was performed of all patients with histologically verified RCC treated at Charles University Medical School Teaching Hospital in Hradec Králové, Czech Republic, between January 1997 and December 2007 with at least 1 course of HAI. No patients were lost to follow-up. One patient (case 1) was previously described in the report of HAI of adoptive immunotherapy[5].

Three patients, all men, with RCC liver metastases were treated with HAI (Table 1). Liver metastases were synchronous in 2 patients and metachronous in 1 patient. In all patients, liver metastases were isolated at the time of therapy. The therapy was administered through a vascular device with a subcutaneous port system that was implanted surgically (in 2 patients) or percutaneously using the Seldinger technique (1 patient) as described elsewhere[6].

The liver metastases progressed rapidly despite therapy in the 2 patients with synchronous liver metastases. In the third patient, prolonged disease control was obtained with HAI of interleukin-2.

Case 1

A 61-year-old man presented in the fall of 1999 with dyspeptic complaints. Imaging studies found a tumor in the left kidney and multiple liver metastases. A left nephrectomy was performed on December 8, 1999. Histology revealed clear cell RCC. Histological examination of a liver specimen confirmed a metastasis of clear cell RCC in the liver. During surgery a vascular device was introduced into the hepatic artery. HAI of interferon-alfa was started on December 20, 1999. A 5-MU bolus of interferon-alfa was administered on December 20 and 21, and the dose was escalated to 10 MU on December 22 and 23. HAI of 10 MU of interferon-alfa was continued on December 27, 1999. Despite therapy, the general condition of the patient declined. He was admitted to hospital on December 28, 1999. Therapy with interferon-alfa was interrupted. Despite supportive care the condition of the patient deteriorated, and he died on January 15, 2000. No autopsy was performed.

Case 2

A 50-year-old man underwent a right nephrectomy and liver resection for clear cell RCC with liver metastasis on July 24, 2000. He was subsequently treated with subcutaneous interferon-alfa (10 MU 3 times a week) and interleukin-2 (1.8 MU 5 times a week). On November 22, 2000 activated monocytes were administered by HAI in a single session, and the patient continued therapy with cytokines. However, disease progression was evident on a control CT scan. The patient was subsequently treated with intravenous gemcitabine, but the tumor progressed and the patient died on February 12, 2001. No autopsy was performed.

Case 3

A 66-year-old man presented in February 2005 with multiple liver metastases progressing on treatment with interferon-alfa. Sixteen years earlier, in 1989, he had undergone a left nephrectomy for clear cell carcinoma and 11 years later, in December 2000, a pancreatic resection and splenectomy for recurrence of clear cell carcinoma. Subsequent to the resection, interferon-alfa was administered. In 2002, the patient had deep vein thrombosis and was treated with warfarin. In June 2004 liver metastases were diagnosed, and the patient was retreated with interferon-alfa. Progression of liver metastases was evident on control CT scan in February 2005. Because no other therapeutic options were available at that time, the patient underwent angiography with embolization of 4 highly vascular metastases on March 2, 2005. The anticoagulation therapy was switched to low-molecular-weight heparin. Subsequently, a vascular device with a subcutaneous port system was implanted surgically into the hepatic artery on March 15, 2005. HAI of interleukin-2 was started in April 2005. The patient was first treated with continuous HAI of 18 MU in the intensive care unit. Subsequently, interleukin-2 was administered as a short bolus HAI of 1.8 MU 5 times a week. The patient tolerated the therapy well, and administration of this interleukin-2 regimen was continued throughout the patency of the catheter until November, 2007. The

Table 1 - Characteristics of the patients

Case	Age (years)	Metastatic interval (months)	Interval from diagnosis to HAI (months)	HAI administration	Regimen used	Duration of HAI	Patient status	Survival after the start of therapy (months)
1	61	0	0	S	IFN 5-10 MU	2 weeks	D	1
2	50	0	4	P	Adoptive immunotherapy	1 day	D	3
3	66	180	9	S	IL-2	2.5 years	D	36

HAI, hepatic arterial infusion; D, died; IFN, interferon-alfa; IL-2, interleukin-2; P, percutaneous catheter; S, surgically implanted port system.

therapy resulted in stable disease that subsequently only slowly progressed. Therapy was continued beyond disease progression as oral tyrosine kinase inhibitors were not available at the time. Progression was very slow and the patient's tolerance to therapy excellent. After the end of HAI the patient was only followed by regular CT scans that indicated stable disease, and it was planned to start therapy with oral multiple tyrosine kinase inhibitor after demonstration of further progression. The low-molecular-weight heparin anticoagulation was switched to warfarin. On April 29, 2008 the patient presented with massive hematemesis of sudden onset. Hemorrhagic shock developed rapidly, and despite aggressive resuscitation with multiple transfusions, the patient died on the same day. At autopsy, a benign gastric ulcer was detected. The ulcer was considered unrelated to the HAI, which was stopped 5 months before the fatal event, and the massive bleeding was considered a complication of chronic anticoagulation therapy. Metastatic involvement was limited to the liver. The liver metastases had been controlled with HAI for 36 months.

The reports on HAI in patients with metastatic RCC are very few[7]. This could be due to a publication bias as sporadic utilization of a treatment method of limited effectiveness would probably result in few cases being considered a therapeutic success meriting publication. To the best of our knowledge, the present series may be one of the largest single-center cohorts of RCC liver metastases treated with HAI. Prolonged survival was observed in 1 of the patients. Although this relatively favorable disease course could be partly due to the long interval between RCC diagnosis and manifestation of liver metastases, this experience indicates that, similar to intravenous administration of high-dose interleukin-2[8], HAI of this agent could result in prolonged disease control.

Although different cytotoxic agents have been used in HAI, the reported experience with HAI of interleukin-2 is limited. The trial reported by Mavligit *et al.*[4] included among 14 patients also 2 patients with RCC liver metastases. No response was observed in either case. The use of HAI of donor lymphocytes after nonmyeloablative transplantation has also been anecdotally documented in combination with radiofrequency ablation[7]. Given the heterogeneity of metastatic sites and disease course in RCC and the relatively low proportion of patients with isolated liver metastases, the effect of HAI on survival would be difficult to evaluate in a prospective manner. Thus, data from retrospective series such as the present one are the only source of information on the specific management of patients with this rare presentation of metastatic RCC. The efficacy of interleukin-2 seems to be dependent on the dose[9,10]. Similar to other drugs[1], HAI of cytokines may result in a greater drug concentration in the tumor microenvironment and less systemic toxicity. The effectiveness of HAI of interleukin-2 may be analogous to the reported efficacy of interleukin-2 inhalation therapy[11].

Until recently, interferon-alfa and interleukin-2 were the only effective agents available for metastatic RCC, as this tumor is resistant to cytotoxic drugs[3]. However, interferon-alfa and interleukin-2 have only a moderate effect on the natural course of metastatic RCC[12,13]. The standard therapy of metastatic RCC has changed. Targeted agents (bevacizumab, sunitinib, sorafenib and temsirolimus) are now known to be active not only in patients failing cytokine therapy, but have also been shown to be superior to cytokines in first-line therapy[14]. Given the success of targeted therapy, other approaches that were investigated in patients failing cytokine therapy, including nonmyeloablative allogeneic transplantation[15,16], inhalational interleukin-2[11] and HAI, now appear only of historical interest. On the other hand, despite the demonstration of the superior activity of targeted agents in the first line as well as the proven effectiveness of targeted therapy in patients failing other targeted agents, this therapy is still not curative, and virtually all patients will ultimately recur. Metastatic RCC is a disease with great variability of manifestations and clinical courses, and individually tailored therapeutic approaches, such as HAI in patients with isolated liver metastases, should not be a priori rejected.

In conclusion, the present experience indicates that HAI of interleukin-2 could be effective in selected patients with isolated liver metastases from RCC, but – like systemic administration – HAI of cytokines is ineffective in the majority of cases.

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New rules on conflict of interest: what has to be done in Europe?

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To the Editor: Conflict of interest has been defined as "a situation in which a person has a private or personal interest sufficient to appear to influence the objective exercise of his or her official duties as, say, a public official, an employee, or a professional"[1]. Conflicts of interest are very frequent in medical oncology: a recent study from the University of Michigan Comprehensive Cancer Center found that nearly one-third of cancer research published in high-impact journals disclosed a conflict of interest[2]. Disclosing conflicts of interest is important, but it is probably not sufficient; efforts need to be directed toward separating research from industry ties. Another important aspect is the presence of members with conflicts of interest in guideline panels; this is a serious issue, also because it is very difficult to demonstrate.

In late April 2009, the Institute of Medicine (IOM) of the US National Academy of Sciences issued a report on conflicts of interest. The IOM rules were summarized as follows in a commentary by Robert Steinbrook[3]:

1. Institutions engaged in medical research and education, clinical care, and the development of clinical practice guidelines should "adopt and implement conflict of interest policies" and "strengthen disclosure policies." They and other interested organizations (such as accrediting bodies, health insurers, consumer groups, and government agencies) should standardize the content, formats, and "procedures for the disclosure of financial relationships with industry."
2. Congress "should create a national program that requires pharmaceutical, medical device, and biotechnology companies and their foundations to publicly report payments to physicians and other prescribers, biomedical researchers, health care institutions, professional societies, patient advocacy and disease-specific groups, providers of continuing medical education, and foundations created by any of these entities." Until Congress acts, "companies should voluntarily adopt such reporting."

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3. Academic medical centers, research institutions, and medical researchers should "restrict participation of researchers with conflicts of interest in research with human participants." Exceptions "should be made public" and occur only if a conflict-of-interest committee "determines that an individual's participation is essential for the conduct of the research" and if there is "an effective mechanism for managing the conflict and protecting the integrity of the research."
4. Academic medical centers, teaching hospitals, faculty members, students, residents, and fellows should "reform relationships with industry in medical education"; these institutions and professional societies should "provide education on conflict of interest."
5. The organizations that created the accrediting program for continuing medical education and other interested groups should reform the financing system so that it is "free of industry influence, enhances public trust in the integrity of the system, and provides high-quality education."
6. Physicians, professional societies, hospitals, and other health care providers should reform physicians' financial relationships with industry; the same standards should apply to community physicians, medical school faculty, and trainees. Physicians should forgo all gifts and other "items of material value" from pharmaceutical, medical-device, and biotechnology companies, accepting only "payment at fair market value for a legitimate service" in specified situations. Physicians should "not make educational presentations or publish scientific articles that are controlled by industry or contain substantial portions written by someone who is not identified as an author or who is not properly acknowledged." Physicians should "not meet with pharmaceutical and medical device sales representatives except by documented appointment and at the physician's express invitation" and should "not accept drug samples except in certain situations for patients who lack financial access to medications." Until institutions change their policies, physicians and trainees "should voluntarily adopt" these recommendations "as standards for their own conduct."
7. Medical companies and their foundations should reform interactions with physicians – for example, by instituting "policies and practices against providing physicians with gifts, meals, drug samples (except for use by patients who lack financial access to medications), or other similar items of material value and against asking physicians to be authors of ghostwritten materials." Consulting arrangements "should be for necessary services, documented in written contracts, and paid for at fair market value." Companies "should not involve physicians and patients in marketing projects that are presented as clinical research."
8. Groups that develop clinical practice guidelines should restrict industry funding and conflicts of panel members. Various entities, including accrediting and certification bodies, formulary committees, health insurers, and public agencies should "create incentives for reducing conflicts in clinical practice guideline development."
9. The governing bodies of institutions engaged in medical research, medical education, patient care, or guideline development "should establish their own standing committees on institutional conflicts of interest" that "have no members who themselves have conflicts of interest relevant to the activities of the institution."
10. The National Institutes of Health should revise federal regulations to require research institutions to have policies on institutional conflicts of interest, including "the reporting of identified institutional conflicts of interest and the steps that have been taken to eliminate or manage such conflicts."
11. Oversight bodies and other groups should "provide additional incentives for institutions to adopt and implement" conflict-of-interest policies, such as by publicizing the names of institutions that have instituted the recommended policies and those that have not.
12. The Department of Health and Human Services and its agencies should develop and fund research agendas on conflict of interest.

The IOM rules seem to be quite strict, but formulating them was an obligatory step because the system was out of control. We hope that in the future such rules will also be applied in Europe. Today conflict of interest is considered more an ethical than a legal issue, and for this reason it is important that new rules be applied and a control system be created to prevent conflicts of interest and, if necessary, proceed through legal provisions. There is no more precious commodity than health, and those in charge of health governance must be free from commercial influence.

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