

Health care and research: Clinical trials in cancer radiotherapy

Through its health programmes, the IAEA has initiated co-operative clinical studies to improve the outcome in cancer treatment

by **Jordanka
Mircheva**

Countries around the world have seen cancer become the number one health concern. Next to accidents, malignant tumours are the largest cause of human death. About 60% of all cancer deaths occur in people over the age of 55.

On the surface, it appears that age is indeed the most important factor for cancer. This is the case only because the older a person becomes, the longer he or she is exposed to agents that directly or indirectly increase the risk of developing a clinical cancer.

Growing cancer burden. Moreover, the cancer burden is expected to increase worldwide if for no other reasons than that more people exist and they are living longer. Indeed, the statistical estimates show that the number of cancer patients may double in the next 20 years just from the ageing of the population.

Apart from the prospect of death, intractable pain, and psychological trauma, the long duration of the disease and its chronically debilitating effects place a serious economic burden on patients and society at large.

Escalating cost. Cancer cure is expensive and the increasing cancer burden is going to escalate the pressure on national social security programmes, which are already under severe strain in many countries. Therefore, from a strategic point of view, it is imperative that greater steps are taken without delay to reduce both the incidence of cancer and its mortality rates.

Cancer prevention. Outright cancer prevention should be the ultimate goal. Certain cancers can be avoided by limiting exposure to carcinogens and risk factors related to lifestyle, occupation, or the environment. It is clear, however, that any implementation of a tentative scenario for cancer prevention by avoiding con-

tact with carcinogens is far from simple. It would be unrealistic to expect a high rate of success, considering that carcinogenesis (the process of initiation, induction, and promotion of cancer) is unlikely to be linked to a universal cause. At the present time more than 60 carcinogenic factors or exposures have been identified as causes of human cancer. Most of these are widespread and include chemicals, ionizing and non-ionizing radiation, certain parasites, and viruses. However, there is no compelling evidence that we have yet identified all of the most important carcinogens. As a matter of fact, the causes for some common human malignancies remain unknown. Regarding cancer prevention, therefore, apart from tobacco smoking, there does not appear to be any other factor which, if avoided, could make a significant dent in the total cancer burden at present.

Education and cancer screening. Public education and cancer screening are of immense importance for the early detection of malignant growth and therefore instrumental in achievement of better therapeutic results. This approach has been strongly advocated and applied in the vast majority of advanced countries. However, it has not yet produced any significant change in cancer morbidity and mortality rates.

Improved therapeutic methods. Importantly, clinical needs have forcefully stimulated fundamental and applied research. As a result, new concepts and agents have been introduced, which in turn have brought about an improvement in therapeutic methods. Nevertheless, it has been postulated that current research in oncology will not have a substantial clinical impact within the next 10 years.

The weapon of targeted therapy. Given the background of increasing cancer burden, and the limits of cancer prevention, screening, and public education, it becomes apparent that today's most promising weapon in the armamentarium against cancer is therapy targeted either

Dr. Mircheva is a staff member in the IAEA Division of Human Health. Full references are available from the author.

at the radical elimination of the tumour or control of its growth. Indeed, early diagnosis and prompt individualized treatment provide cancer patients with the best chance of surviving the disease. With each passing year, more patients with cancer are curable and treatments are associated with less morbidity than in the past. During the last few decades, the cure rate of cancer patients in industrialized countries has slowly but steadily increased from approximately 25% (in 1950) to about 50% (in 1985). It should be recognized that this progress has been due not only to early diagnosis, but also to a gradual improvement of the main modalities of cancer treatment — surgery, radiotherapy, and chemotherapy.

Surgery is the classic method of cancer treatment. It is associated with a high rate of cure in early stages of the disease, when adequate resection of the tumour can take place, even with the price of anatomical deformity and perhaps physiological impairment. Unfortunately, in the majority of cases, diagnosis is made in more advanced stages, when tumour microextensions and regional or systemic metastases present limits to the success of surgical treatment.

Radiotherapy in cancer management

In the treatment strategy against cancer, radiotherapy is the second most important modality after surgery and it has the potential to become an even more important factor. Its main goal is to deliver a precisely measured dose of ionizing radiation to a defined tumour volume so as to destroy cancer cells while inducing minimal damage to surrounding normal tissues. In addition to its curative effects, radiation plays a major role in the palliation of the disease and thus improves the quality of life that remains.

In the future, organ preservation in cancer treatment will assume greater importance, which will significantly augment the role of radiotherapy, particularly for patients with head and neck tumours, carcinoma of the breast, oesophagus, soft tissue sarcomas, carcinoma of the rectum, anus, vulva, and paediatric tumours.

The last two decades have witnessed considerable advances in the radiation treatment of cancer, with cure now being a realistic therapeutic objective. More precise, accurate, and reproducible ionizing radiation delivery systems have been introduced, as have better diagnostic procedures and computerized treatment planning, for example. At the same time, important knowledge about radiation therapy physics and greater understanding of clinical radiobiology phenomena have been acquired. These biological and technical developments in cancer

radiotherapy have resulted in substantial improvements of survival rates for patients with Hodgkins' disease, cervical carcinoma, carcinoma of the endometrium, seminomas, and carcinoma of the larynx.

Unfortunately, in a large proportion of malignant neoplasms, local recurrence and distant metastases still are frequent. Radiation therapy's inability to control the disease process is clearly evident in patients with advanced stages of malignant tumours of the head and neck, gastro-intestinal tract, gynaecologic system, skin, bones, soft tissues, etc.

Therefore, specific efforts have been directed towards improving the potential of radiotherapy for local and regional control of cancer through development and investigation of multiple therapy strategies. New techniques for administering conventional radiotherapy have been introduced and supplemented by methods which can be used to modify the response of tumours and normal tissues to radiation. These techniques include changes in the dose rate, combined modality treatment involving cytostatics, sensitization by drugs, or heat, among others. Novel types of radiation having physical and biological advantages — such as fast neutrons, protons, light and heavy ions, and negative pions — are now available.

However, these new concepts and treatment approaches may become effective weapons against cancer and be introduced into routine clinical practice only through fastidious and conscientious clinical studies.

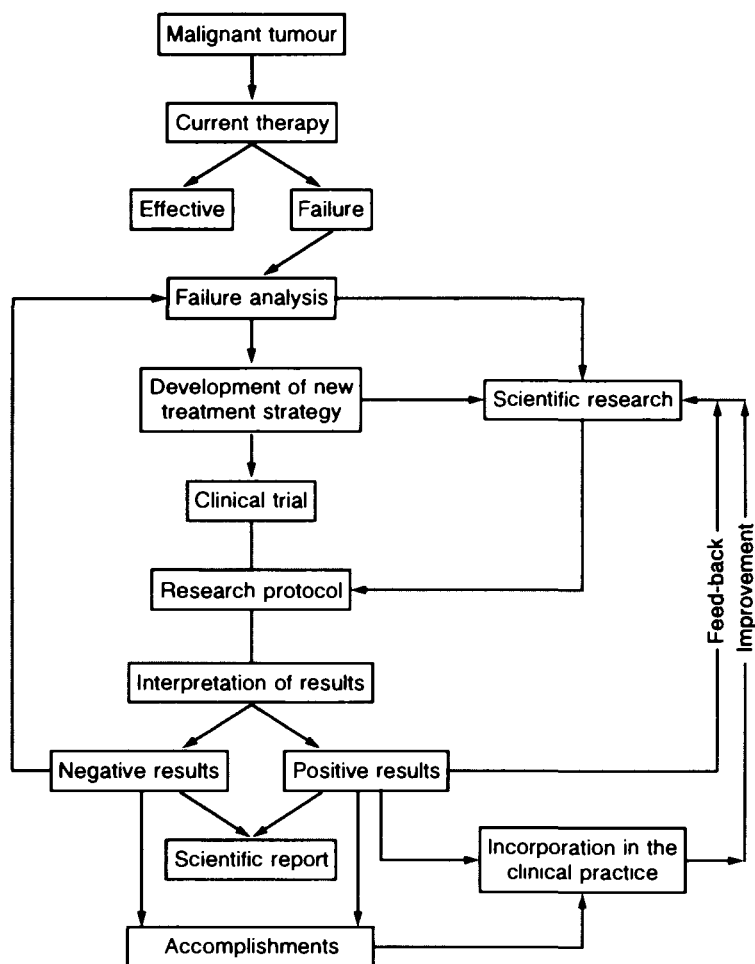
Clinical trials in cancer radiotherapy

With the current state of knowledge, it appears that numerous therapeutic methods can help control malignant growth, yet they still fail to eradicate the tumour. Therefore, as previously noted, only new treatment strategies based on advanced concepts could have an immediate impact on cancer morbidity and mortality rates.

Clinical trials are the most important (if not the only) methodology for validating the efficacy of any new therapeutic intervention. The clinical trial is a relatively recent phenomenon in the history of medical practice. Well-conducted trials have been undertaken only in the past 40 years. Before the era of modern clinical trials, treatment decisions were largely based on faith and tradition, reverence for authority, or simply anecdotal observation. Recently, there has been a large increase in clinical trials due to the development of many new treatment strategies.

The evaluation of a treatment strategy can be accomplished either by retrospective study (if

Key Elements in the Process of Cancer Radiotherapy Clinical Trials



Many elements are involved in properly conducting a clinical trial. Among the most important are the research protocol. It needs to define the trial's objectives; tumour type; stage of disease; treatment programme; quality assurance criteria; procedures in the event of toxicity; criteria for response; review procedures, including ethical review; installment of data centre; recruitment of clinicians and patients; the eligibility of patients; informed consent requirements; data acquisition; and statistical analysis. The clinical trial's accomplishments include improved performance of radiotherapy; better therapeutic rates; the transfer of skills and knowledge; the implementation of quality assurance; improved competence in both clinical and statistical terms; scientific achievements; unbiased results; and savings of time and money.

the treatment concerned has been tried in the past) or with a prospective clinical trial. A major disadvantage of the retrospective studies is the existence of serious biases in the analysis and interpretation of results. This is often due to lack of uniformity in patient selection and treatment procedures, as well as the existence of numerous undocumented facts or factors.

Contrary to the above, the major strength of prospective clinical trials is that the objectives are clearly defined in advance and patients are selected and treated accordingly. The data are also evaluated in a uniform way to ensure that the results are unbiased.

Basic principle of clinical trial. The basic principle behind a cancer clinical trial is to provide specified types of patients with the best known treatment in a preplanned manner and under controlled conditions. The clinical trial thus will allow reliable conclusions to be drawn that can subsequently be applied for the benefit of future patients.

Clinical trials are ethical only if the foreseeable risks are justified in terms of the anticipated benefits to the patient and the community. However, it is unethical to launch a trial if it does not have a chance of attaining the predetermined number of patients to ensure the statistical significance of results; e.g. reliable conclusions. Only a few institutions by themselves can have enough cases over an acceptable time period to establish with certainty and statistical significance the value of a selected treatment regime.

This emphasizes the necessity of conducting multicentre co-operative clinical trials to ensure entrance into the study of the requisite number of patients. The vast majority of multicentre trials are performed by different national institutions. From an international perspective, only the Treatment Branch of the European Organisation for Research and Treatment of Cancer (EORTC) is involved with the conduct of cancer clinical trials in European Union countries and Switzerland. It is of interest to note that of the 282 total EORTC cancer clinical trials active in 1992-93, only 35 deal with the application of radiotherapy in cancer treatment.

In the periodic analysis of cancer clinical trials published by national or international institutions, it is frequently indicated that although the outcome of cancer patients is better if they are treated in a clinical trial, only a fraction (usually less than 10%) of available patients are entered into the study. The insufficient number of cases is the number one obstacle in successful completion of even multicentre co-operative trials.

This lack of patients for trials reflects the existence of a very strict exclusion criteria. On the other hand, it is in accordance with the main eligibility rule for participation in a clinical trial, postulating that each patient should be given individually the best known treatment. In industrialized countries, the majority of cancer patients report to a doctor usually in a relatively early stage of the disease, when the best known

treatment is surgery, alone or combined with conventional radiotherapy and/or standard chemotherapy. On the contrary, in developing countries, most patients report at very advanced stages of the disease, when the prognosis is very poor and the chances of improvement by application of the classical methods of treatment is minute. This warrants consideration for designing cancer clinical trials that can jointly include medical teams from radiotherapy departments in developed and developing countries alike.

The IAEA's present and potential role

Seen within this perspective, the IAEA has a unique opportunity to contribute towards improved cancer control, especially in the developing world. Specifically, it can serve as a mechanism through which countries can participate in cancer radiotherapy clinical trials, and it can help ensure the enrollment of the required number of patients. This can be done through creation of an international group of oncological teams from selected centres in developing IAEA Member States and experienced teams from advanced countries, both with an interest and strong scientific and clinical background for participation in a clinical trial.

An existing IAEA avenue for such co-operative work — co-ordinated research programmes (CRP) — can be used to both promote the research and to help ensure the effective transfer of knowledge, skills, and awareness of this methodology in developing countries. The results then become of value to all IAEA Member States.

The successful implementation and completion of a co-operative clinical trial in cancer radiotherapy relies upon the appropriate design of the strategy of treatment, standardization of patient selection, and uniform compliance with a set of carefully defined therapeutic guidelines. In that way, all patients in the study will receive essentially equal treatment regardless of which participating centre enters their case. Therefore, a research protocol must be carefully designed and adopted by all participating parties. Its structure should spell out clearly the objectives of the study, the patients eligibility (including exclusion criteria), the exact type of malignancy and the allowable stages of the disease for the study, the exact details of the therapeutic regimens to be followed, criteria for quality assurance evaluation, criteria for response, procedures in case of toxicity, and statistical methods for evaluation.

Strictly following such a carefully designed treatment protocol, based on the latest scientific and clinical achievements of oncology, will hold

many benefits. It should not only help improve the performance of radiotherapy on selected tumours, but it should also serve to enhance the competence of participating parties in the field.

IAEA-supported clinical trials in cancer radiotherapy. A number of IAEA-supported clinical trials are in progress through the mechanism of co-ordinated research programmes.

One is on the clinical application of radiosensitizers in cancer treatment. It is directed towards enhancing the therapeutic gain induced by radiation in advanced cervical carcinoma by the introduction of an hypoxic cell radiosensitizer in the therapeutic management plan.

It is tacitly believed that one reason for failure in cancer radiotherapy is the existence of hypoxic cells that usually compose about 20% of the solid tumours. They are considerably more resistant to radiation-induced cell killing than the well-oxygenated normal cells. It has been found that about three times the radiation dose is required to achieve the same proportion of cell killing for hypoxic cells when compared with well-oxygenated cells.

Although the exact role of hypoxic cells in the failure of radiation to cure tumours is not yet completely known, specific efforts have been directed towards developing drugs that can effectively sensitize hypoxic cancer cells to radiation. In this way, the likelihood of a positive outcome from tumour radiotherapy is improved. The major class of drugs of clinical interest has been the nitroimidazole compounds, with the most examined agent being misonidazole (2-nitromidazole).

Unfortunately, the overall evaluation of results of 33 clinical trials with misonidazole suggested problems. They demonstrated that the possible benefit from the use of this drug in combined cancer treatments involving radiotherapy can be achieved only in a small proportion of cases — mainly head and neck tumours — due to the development of peripheral neuropathy in about 50% of the patients. The problem is that the dose-limiting neurotoxicity of the drug is manifested at a cumulative dose level below which clinically detectable hypoxic cell sensitization cannot be produced. Subsequent developments of hypoxic cell sensitizers included the synthesis of a series of 2-nitromidazole analogs that might be superior to misonidazole in terms of pharmacokinetic, radiosensitizing, and toxicological parameters.

The data presented in scientific literature clearly illustrate that the nitrotriazole derivative known as AK-2123 is an hypoxic radiosensitizer with lower neurotoxicity than misonidazole and with a higher sensitization enhancement ratio under the clinical context.

Paraclinical and clinical results obtained and published by 25 teams from 11 countries indicate a possibility for enhancing the anti-tumour effect of ionizing radiation for certain types of tumours by AK-2123. However, there is an unquestionable need for further systematic studies on toxicological and pharmacological properties of AK-2123, so that a reliable conclusion for the clinical usefulness of the drug in sensitized radiotherapy of tumours can be drawn. This task is an important clinical/scientific area of concern not only for developing countries, but also for industrialized ones. The IAEA-supported CRP, through which a well-designed multi-centre controlled clinical trial can be conducted, offers a good strategy for helping countries achieve beneficial results.

The second CRP is a randomized clinical trial of radiotherapy combined with mitomycin C in the treatment of advanced head and neck tumours.

The squamous cell carcinoma of the head and neck is a common malignancy worldwide with a very poor prognosis for patients with advanced tumours. A large majority of patients die from uncontrolled local disease (tumour persistence/recurrence). The surgical resection followed by post-operative radiation therapy remains one of the most commonly employed management strategies for patients with locally advanced but technically resectable malignancies. However, even with these aggressive treatments, about 50% of patients will experience the local/regional relapse.

The primary control of the tumour, and sequentially the survival of the patients, might be improved if an appropriate cytotoxic drug could be given concurrently with irradiation to enhance the radiation effect. Mitomycin C has been shown to be preferentially toxic to hypoxic cells. Theoretically, the concomitant administration of mitomycin C with its selective toxicity towards hypoxic cells, and the radiation therapy with its maximal effectiveness against well-oxygenated cells, should result in an enhanced therapeutic ratio.

Over the past 12 years, two consecutive randomized clinical trials have been conducted to assess the effectiveness of mitomycin C as an adjunct to radiation therapy (applied alone or in combination with surgery) in patients with squamous cell carcinoma of head and neck. The analysis of results obtained so far suggests that mitomycin C improves the radiation-induced local tumour control without enhancing the normal tissue radiation reactions. However, the number of patients entered into the study until now is not sufficient for statistical validation of the results. Through the organization of a multi-

centre clinical trial, the IAEA's CRP can help obtain valuable information regarding the therapeutic benefit in adding mitomycin C to radiotherapy for the treatment of advanced carcinoma of the head and neck tumours. It can also make available the requisite number of cases, so that the results are statistically validated.

The IAEA also has initiated a CRP clinical trial involving the application of radionuclides. Radionuclide therapy with open sources has gained renewed momentum with the availability of new radiopharmaceuticals. The CRP is directed at the use of strontium-89 (Sr-89) and phosphorus-32 (P-32). It seeks to comparatively assess the relative merits of Sr-89 and P-32 in terms of their efficacy and toxicity when used in the palliative treatment of painful malignant bone metastases.

P-32 has been in existence for more than 25 years and it is relatively inexpensive and widely available. Sr-89 is a recent radiopharmaceutical which is very expensive and restricted in availability. Both radionuclides have claimed comparably efficacy, but P-32 is believed to be more toxic to the bone marrow. No comparative evaluation has been made of these agents so far.

The outcome of this randomized controlled clinical trial will have meaningful impact on the use of these agents in developing countries and wherever cost-benefit ratio is an important consideration in health care.

In summary, the IAEA's programmes in cancer radiotherapy are aimed at conducting high-quality clinical trials. This means that the studies address a clinically vital question, are randomized, have a sufficiently large sample size, and conform to high standards of quality control.

Achievements and benefits

The key element of the IAEA's co-ordinated research programmes in cancer radiotherapy is the research protocol. It outlines the study's objectives and clarifies the mechanisms of its implementation in clinical practice.

In actual terms, the research protocol is a reflection of the latest scientific achievements in oncology. Strictly following the protocol should guarantee the successful implementation and completion of the IAEA's proposed programmes. This, in turn, will improve the performance of radiotherapy, e.g. cure rates and survival of cancer patients, and increase the competence of participating parties in the field and encourage a wider use of this multimodal approach in oncological practice, particularly in developing countries. □