COMBINED TREATMENT STRATEGIES – EVOLUTION OR REVOLUTION IN ONCOLOGY

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A major milestone in oncologic surgery was the radical mastectomy, which was introduced by Halsted for the management of breast cancer. Eagerness in the improvement of micro- and macroradicalism resulted in an increasing precision of qualification criteria, modifications and new surgical techniques. In very advanced solid tumours, which previously disqualified patients from radical treatment, reconstructive and microvascular surgery provides a chance for local tumour control with a good functional and aesthetic effects (1). Histoclinical knowledge of subclinical disease leads to elective, selective and conservative surgical techniques (2). For many decades, surgery has been recognized as an independent leader among treatment methods in oncology. Therefore, it should not be surprising that such leadership is still often preferred by some clinicians (3).

The first and major milestone in radiotherapy occurred in 1922 when Coutard proved that advanced laryngeal cancer could be cured without disastrous late sequelae using fractionated small daily doses of radiation instead of a large single dose (4). This resulted in rapid developments in radiobiology and medical physics. From 1950 to 1960, almost all current radiation techniques were developed (5). Fast progress in technology resulted in cobalt units followed by linear accelerators with high-energy photons and electrons. Radiation therapy became more precise, offering new three-dimensional conformal, stereotactic, gating and dose intensity modulation techniques. A common baseline is to escalate the dose within the tumour and protect critical normal organs as much as possible.

A milestone in clinical oncology was the development of polychemotherapy for Hodgkin’s disease. Chemotherapy for non-Hodgkin’s lymphoma and leukemia has become a major, and often the only therapy, with a supportive role for surgery and radiotherapy. After ignoring the role of chemotherapy for solid tumours for a long time, new agents such as adriamycin, cisplatin, nitroimidazoles, and taxanes resulted in its unquestioned place within combined treatment strategies. This was accompanied by intensive progress of pharmaceutical marketing with new molecular modifiers and inhibitors with easily forgotten trademark names. Although the efficacy of these new “nib-mabs” agents is not proven and well documented, they are illusorily advertised as a new “gold” drugs for saving lives.

Three major periods can be defined in the history of cancer therapy. The first period is defined when almost all the revolutionary methods were initiated. During the secondo one when according to Vincent de Vita, progress in oncology was continued by gradual small-step improvements in the treatment outcome. Knowledge and experience gathered in these two periods has led to the beginning of the third period, with enormous intensification of experimental and clinical research in the last 10-15 years, which has yielded fascinating intellectual and scientific future possibilities. The results of long-term clinical studies convincingly suggest that efficacy of surgery, radiotherapy and chemotherapy have reached a plate-
In order to escape from this therapeutic trap, clinicians are motivated to collaborate with genetics, radiobiologists, and molecular biologists. Clinical language is slowly changing and it is enriched by terms and criteria that, until recently, were used in basic and experimental research.

Histoclinical criteria for individual optimization of combined treatment strategies are recognized as insufficient. For this reason, clinicians are becoming more and more interested in genetic and molecular mechanisms controlling tumour growth. For more than 10 years, some dogmas used in the clinic were questioned and verified. This seemingly may be the result of technological progress. However, precise tools given to radiation oncologists require much experience and many skills, and also enormous responsibility and criticism, and a chance of success should be weighed against the risk of failure. Functional-imaging (CT, MRI, PET), as well as other tools monitoring conformal radiotherapy, seem to be a tempting option replacing the clinician’s mind and experience. However, it should be remembered that they are only one of many elements of combined therapy. Quality of life and organ preservation have become essential for treatment outcome. Therefore, except for a few clinical situations, surgery-radiotherapy-chemotherapy relationships are considered more and more often as cooperative rather than competitive. Surgery and radiotherapy provide local effects, while a systemic effect is expected from chemotherapy. Until the mid-1950’s, only a small number of cytotoxic agents were available, and therefore, chemotherapy for solid tumours was likely considered as a palliative modality and usually followed surgery and radiotherapy. Despite tremendous progress in chemotherapy, it is surprising that such a sequence still remains in the mind of some clinicians, mainly non-oncologists.

Bio-clinic of malignant tumours

Generally, growth of solid tumour is subdivided into two periods: subclinical and clinical. During the first period, the tumour is growing as a single lesion, but sometimes its genetically-modified cells escape and initiate metastatic lesions. To reach the level of clinical detection for a tumour of about 0.5 cm³ (fig.1), containing 10⁸-10⁹ cells, 27-28 cell doublings are needed. The interest in this period was neglected because there was a belief that elective surgery or radiotherapy is sufficient to eliminate subclinical lesions. Currently, the risk of subclinical disease is still estimated empirically.

Larger interest has been focused on clinical tumour growth. During this period, no more than 8-9 doublings (assuming an average doubling time of about 2 months) results in a tumour the size of 6-7 cm in diameter, often with metastatic lesions in regional lymph nodes. Simultaneously, tumour growth becomes slower. In such an advanced stage of disease, only palliative treatment is available and the chance of permanent cure is almost definitely lost. Sometimes, surgical cytoreduction can reduce the tumour size to a level that makes radical treatment possible, unless distant metastases have already developed.

The clinical part of tumour growth clearly shows that the period available for radical treatment is relatively short (about 15-18 months), and is of crucial importance for clinicians. Until the end of the 1980’s, there was a belief that, because clinical growth of solid tumour is generally slower with a volume doubling time of 2 months, there is no risk to continue its growth during the treatment completed within

![Fig. 2. Scheme of natural growth of solid malignant tumour and its response to the treatment modalities (CH – surgery, RT – radiotherapy, CT – chemotherapy). Black dots within tumour circles are the symbols of clonogenic cells. Permanent cure is the result of death of all potentially or actually proliferating tumour cells. Complete tumour regression is not a prerequisite of permanent cure because subclinical lesion(s) may still contain from 10¹ – 10⁸ cells. The more cells they contain, the sooner recurrence will occur and its growth is about 6-10 times faster than that of the primary origin. Surgery and radiotherapy do not affect metastatic lesions, and in order to eliminate them, chemotherapy should be used.](image-url)
that time. This dogma has unfortunately been promoted by clinicians for many years. However, it was recognized and well-documented that both mechanical (surgery), and physical and chemical cytotoxic intervention (radiotherapy, chemotherapy), except for the cell kill effect, induce the opposed effect of accelerating the repopulation of surviving clonogenic tumour cells. The speed and number of cells participating in this process increase during the treatment. As the result, doubling time may shorten to 3-4 days. Therefore, during week six of radiotherapy, repopulation is so effective that it can counterbalance the cell kill effect of daily doses of radiation. The same process occurs after chemotherapy, but not during short-time surgery for chemotherapy. If tumour cells survive in surgical margins or in small aggregates beyond surgical bounds, they begin to repopulate rapidly with a doubling time of about 8-12 days. The rule that radiotherapy can be started up to 3 months after surgery is no longer rational, and it should begin as soon as catabolic processes caused by surgery are compensated (6).

Tumour biology has proved that it is naïve to assume a regular spheroid shape of the tumour, and its cellular spread beyond the tumour burden can be easily missed during locally-focused modalities (surgery, radiotherapy). Knowledge of tumour biology also allows the questioning of complete tumour regression as an early pre-requisite for long-term tumour cure. For surgeons, complete tumour excision with negative margins is an obvious attribute of radicalism. The surgeon excises the entire tumour and tumour bed. Meanwhile, in radio- and chemotherapy, complete regression is the result of depopulation by only 3-4 logs of tumour cells (fig. 1 – dotted line), although 6-7 logs of tumour cells may remain alive. To cure patients, it is important to kill these cells and to kill them all. In oncology, cell kill means permanent loss of proliferative activity forever, although some of the cells can functionally be active. Gladstein has pointed out that “patient and tumour cells both die only once”, and it is important to kill all of the tumour cells, but to keep the patient alive until his or her natural death (6).

Therefore, complete tumour regression should be considered as a misleading prerequisite of treatment efficacy. In subclinical regimen of decimated but still survived tumour cells will awake and begin to proliferate faster and faster with increasing its number and aggressiveness. Biologically, it is not the same tumour as it was at the beginning of treatment (fig. 1), as it contains only aggressive and proliferating tumour clonogens. The more aggressive these cells are, the sooner local recurrence will occur. Eradication of such lesions is more difficult than the primary lesion and requires a more aggressive therapy. The situation becomes even worse because the primary lesion and subclinical survivors can produce genetically modified metastatic cells that leave the primary site. It is almost impossible to predict whether these cells are released during the subclinical or clinical period.

Tumour biology and genetics have led to the understanding of tumour cellular heterogeneity and its differences in sensitivity on treatment outcome. Currently, all therapeutic strategies remain focused on the entire tumour, assuming homogenous cell distribution and its sensitivity to the treatment (tumour-targeted therapy). Meanwhile, biologists try to convince clinicians that only some subpopulations of tumour cells should be therapeutic targets and their sensitivity may differ significantly (tumour-cell-targeted therapy). These subpopulations, which keep tumours alive, are quiescent clonogenic proliferating, hypoxic and endothelial cells. The architecture of these sub-targets is not regular but individually changing, even during the treatment. Some of these populations are very dangerous, e.g. endothelial cells of pathological vessels that proliferate about 1000-times faster than those found in normal vessels. Currently, hypoxic, proliferative and angiogenic targets can be identified in vivo by

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Fig. 1. Scheme of therapeutic strategies in oncology: (a) – sequential, (b) combined with restricted timing
special PET tracers. This creates a promising perspective for more effective therapeutic modalities targeted specifically against hypoxia, proliferation and/or angiogenesis of malignant tumours. Some of these modalities have already been tested using molecular inhibitors and modifiers combined with traditional therapy.

Radio-chemo-surgery – evolution or revolution

Knowledge regarding the unfavourable effect of accelerated repopulation has convinced clinicians that therapy timing is a major prognostic factor for treatment outcome. Its importance has been proven by the poor results of protracted radiotherapy, neoadjuvant and adjuvant chemotherapy. All of these studies lead to the clinically important rationale that once the treatment is commenced, it should be completed as soon as possible, whether or not it is a single or combined modality. Although the strategy of sequential therapy is still used (fig. 2a), it is no longer justifiable, and it should be replaced by a combined therapy strategy including concurrent radio-chemotherapy (fig. 2b). It suggests that such a strategy should be individually designed concerning methods, its sequence, timing and intervals between treatments. However, it should be remembered that the rate of tumour control lost by each single day of extension of the treatment is higher than the rate of tumour control benefit achieved by shortening the treatment by one day. This non-linear relationship means that time-ignorance costs the patient more than the effect made to keep treatment time tight.

The combined treatment strategy should be designed a priori and accepted by a site-team specialists. For example, if a specific strategy consists of surgery with post-operative concurrent radio-chemotherapy, the first step is to reserve the beginning of radiotherapy in the centre, which can also provide chemotherapy. The next step should be to tailor the time of surgery including postoperative interval, but never in reverse. Such a treatment itinerary provides higher quality and efficacy in oncology and is defined as a “theragnostic oncology” (from the Greek term: therapia and gnosis – know how to treat, whom, and when). Treatment efficacy depends not only on optimal choice of combined methods and its sequence, but also on the quality of its realization. Poor quality of one method is sufficient to jeopardize the whole expected benefit to the patient. This is obvious as a well-experienced oncologic surgeon, radiation oncologist and medical oncologist ensure higher quality and effectiveness of treatment compared to a young inexperienced team, especially if a non-oncologic surgeon performs some operation incidentally.

Theragnostic combined treatment strategies

Theragnostic treatment strategies (7) no longer remain as theoretical concepts but are already evidence-based achievements. Some are presented in table 1. The combination of different time-restricted treatment modalities and techniques can likely result in pronounced therapeutic gain and survival. Concurrent radio-chemotherapy and intraoperative radiotherapy, using highly specialized conformal techniques and reconstructive surgery is more and more often used in daily practice. Currently, many patients previously qualified to palliation have a chance to be cured. One of the most spectacular achievements is stereotactic radio-neuro-surgery (SRNS) for brain tumours (8). The SRNS network is already working at the Institute of Oncology in Gliwice in collaboration with Dep. Neurosurgery Silesian Medical Academy. The team, consisting of a neurosurgeon, -diagnostics, -pathologist, -biologist and radiation oncologist, qualifies patients to the treatment (fig. 3). Functional Fiber-Tracking MRI provides serial images for three-dimensional reconstruction of brain tumour position in relation to brain tracts and centres.

Fig. 3. Scheme of stereotactic radio-neuro-surgery network for brain tumours therapy
Images are digitally transferred to the operation theatre and to a neuronavigation system. Under imaging and visual control with on-time video recording, the tumour is excised without damage to the central tracts and centres. The practice shows that the shortest access to the tumour is not always the best one. Surgical video-records and images are reversibly transferred to the planning of stereotactic radiotherapy with as many different-angle beams as needed. Stereotactic irradiation is therefore focused on the tumour bed and margin regions. The SRNS network is directed by the BrainLab System. Such a combined treatment network results in a decrease in the risk of serious neurological postoperative complications by 30-40%. Another example may be the use of Biological PET imaging for individually modified escalated radiotherapy for prostate cancer in one of the US centres, which increases the 5-year disease-free survival to 98%. Theragnostic and combined therapy results in gradual progress toward individually optimized treatment methods.

Are the actual diagnostics and therapeutic criteria precise enough to achieve benefits in theragnostic oncology?

It is unreasonable feeling that the technical and computerized revolution in diagnostics and therapy can be used as a tempting excuse and alternative to experience, skills and professional intuition of the clinicians. However, the question arises whether oncologists have histoclinical and therapeutic criteria precise enough to dominate over the technology. It is likely that they do not. The TNM (AJCC) system is still used in the clinic to establish staging of the tumour. However, each of the T or N category includes a group of tumours (nodes) heterogeneous by their volume. For example, in the T2 stage group of tumours, this volume can differ by a factor of eight. Meanwhile, the cell killing effect of radiotherapy of cytotoxic agents is measured in relation to the initial number of...
more and more popular criterion is “progression-free survival”, which allows scoring of responding patients who have not necessarily achieved a complete or partial remission. Easson proposed that cure can be considered when the survival curve for treated cancer patients becomes parallel to the survival curve of healthy individuals (5). Although such a definition might not be satisfying, it suggests that at least some types of cancers can be treated as other chronic diseases. A cure might not be the only goal to achieve, especially if chances are poor, and keeping patients alive in good comfort should not be ignored (5, 12).

Unequivocal interpretation of the criteria for treatment efficacy is essential, especially if it is used in evidence-based studies. There is a belief that statistical significance is crucial for evidence-based standards. To achieve the level of \( p=0.05 \) for therapeutic gain, a large number of patients should be enrolled in the study. What happens when six (\( p=0.06 \)) instead of five patients failed to respond to a specific treatment method? Does it mean that this method should not be accepted because only 94 patients responded well? Statistical significance does not necessarily mean clinical importance. In many controlled studies, therapeutic benefit is lower than expected, and, in meta-analyses it is even much lower. These studies are a main source of evidence-based standards. However, they include an enormous heterogeneity of patients and tumours. Generally, these studies are focused on universal “gold standards” for specific tumour type, and they offer an average result ignoring its biological heterogeneity. This
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seems to be its major weakness. Even if the “average” benefit is high, e.g. 90% chance to be cured, the patient often asks: “Am I in the 90% cures or in 10% of failures?” There is no answer to such a question. The risk is not evenly distributed among all the patients and for the individual, it is always all or nothing” phenomenon. Therefore, it does not seem logical to recommend averages as universal standards. It is important to remember that the standards should be used as general guidelines, but not necessarily as specific “roads” to reach the goal, which is to cure the individual patient. Oncologists should be aware that sophisticated and computerized technologies are only the tools, and by using them together with standards, they can be at most a craftsman. Theragnostic oncology consists not only of knowledge, but also of skills, experience, logic and common sense which, if properly used, allow individualizing treatment strategies to achieve “sum-mum bonum” for the patient, which is permanent cure. This may change profession into medical art, which is probably best illustrated by an old Arab proverb – “A single talk with a prophet means more than 5 years of studies”.

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