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Review article

Radiotherapy

Have innovations in radiotherapy for head and neck cancer improved the curability of the disease?

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In an era of distinct technological innovations in radiotherapy, a clinically important question has arisen: can the increase of radiotherapy (RT) effectiveness be attributed to these innovations, at least in the case of head and neck (H&N) cancers? In order to answer this question, 133 studies were published, including 21,058 patients who were selected for the present survey with H&N cancer treated within the period of 1970–2010. Three end-points, e.g. 5-year local tumor control (LTC), disease-free survival (DFS) and overall survival (OS) and their average values were evaluated over the consecutive decades. For cancer in the early stage, both LTC and DFS were constantly high (80–90%) through the analyzed decades. For locally advanced cancer, average rates of LTC and an DFS were also constant, but much lower than expected (40–45%). The OS had an increasing tendency: from 45–50% in 1980 to more than 70% in 2010. It may suggest that during the 5-year follow-up period, some proportion (~20%) of advanced tumors gradually progressed from local to chronic disease. Various technical and clinical problems influencing the results of the present review are discussed in detail. Some uncertainties and doubts regarding the RT trials may suggest that "evidence based" recommendations might not be satisfactory, as in the era of combined treatment modalities; it may seem reasonable to replace them with "individually personalized combined therapy". However, nowadays the only plausible solution to improve H&N cancer curability is to intensify all efforts to detect it in the very early stages of the disease and to increase various activities to convince people to participate in regular prophylactic examinations.

Key words: head and neck cancers, local tumor control, disease-free survival, overall survival end-points, early cancer diagnosis, permanent curability

Technological revolution and innovations

The era of orthovoltage radiotherapy (RT) and the Ralston Paterson "school of radiation dose delivery" [1] lasted for over 60 years. During these years radiotherapy planning was relatively simple: based on X-ray radiographs and 2D-coplanar, geometrically regular, well-shaped 2–6 beams focused on the tumor (fig. 1), whilst dose distribution was calculated based on diagrams of the percentage depth isodoses.

During the 1970s, cobalt units were gradually replaced by high-tech linear accelerators (Linacs), offering a wide range of MV

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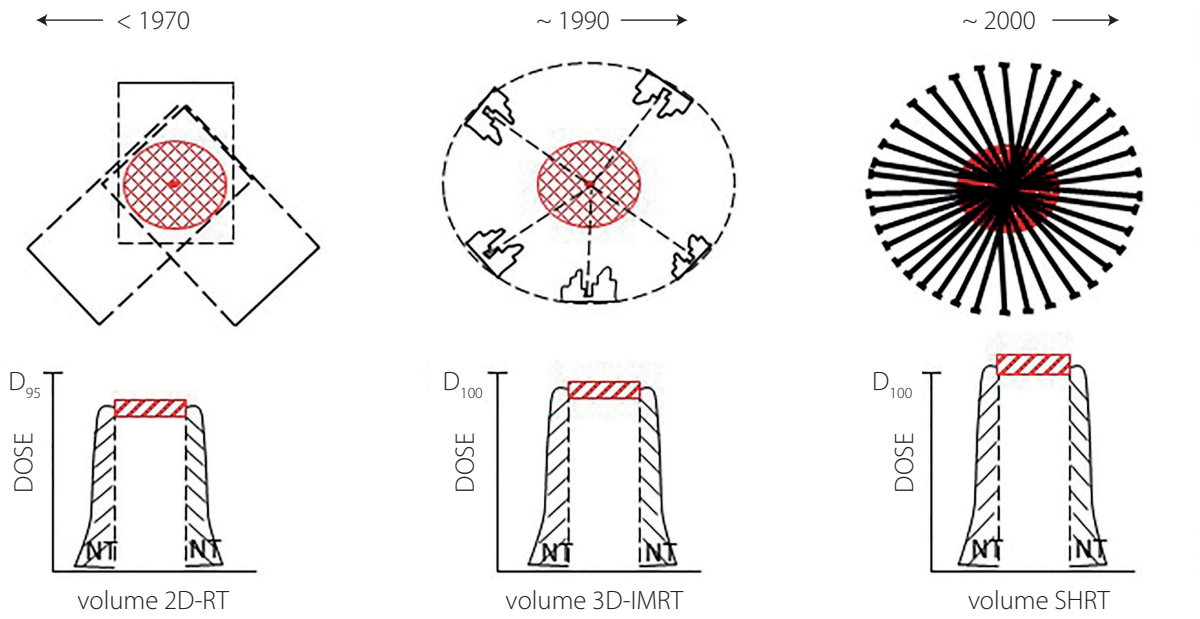

Figure 1. Schemes of three different techniques used in radiotherapy during <1970 and >2000 year with respective dose distribution within the tumor (T) and in the surrounding normal tissues (NT). 2D-RT – two dimensional nonconformal RT; 3D-IMRT – three dimensional dose intensity modulated conformal RT; SHRT – stereotactic hypofractionated multidimensional, conformal RT

energy (5–>20 MV) photon and electron beams. As opposed to Paterson's principles, Fletcher's rules were based on radiobiological principles, and have been universally accepted [2]. Linacs were gradually enriched with multileaf collimators (MLC), cone-beam CTs, real-time tumor tracking, fusion of the CT and Linacs (tomotherapy). Corollary to these technological innovations, RT planning has begun to use precise 3D-conformal IMRT, IGRT, IART, respiratory gating RT, biologically targeted IMRT [3–14], defined by Coleman et al. [12] as SMART radiotherapy. Irregular beam shapes made it possible to tailor the radiation dose which was focused both on the tumor and its margins, with a sharp decrease of radiation beyond this area (fig. 1). However, clinical practice has shown that this comprehensive and powerful solution is in fact a sword of Damocles. On the one hand, conformal techniques offer a substantial decrease in the dose deposited in the surrounding healthy tissues, and therefore reduce the risk of serious late complications., whilst on the other hand there is a risk of cold spot(s), even small ones, in the tumor volume, due to the dose within the tumor; this is likely to lower the preliminary predicted probability of local tumor control [14].

Such technological and systemic innovations [3–14] in three-dimensional RT has opened the possibility for various altered dose fractionation schedules used either alone or combined with other therapeutic modalities like surgery or chemotherapy [12, 15–17]. Moreover, proton and boron therapy have appeared, yet their set up is extremely expensive so the practical use is still somewhat limited. The next interesting option, increasingly growing in popularity, is stereotactic hypofractionated radiotherapy (radiosurgery, SHRT, SHRS) [18–20]. Although its principles were already defined in 1948 by Takahaschi [8], SHRT has been widely used only since 2000, mainly due to special modifications of the Linacs (VMAT) and the new robotic CyberKnife. A key-principle of this method is the use of many (even more than 100) pencil beams focused on the tumor, with a sharp down dose gradient beyond its bounds (fig. 1). SHRT is an example of a "round game" in radiotherapy, meaning the return of RT to its roots, when in the 1900s, single or a very few large dose fractions were being used. This method was, however, quickly abandoned because of the very high incidence of lethal late complications. After more than 100 years, it came back to the RT arena, offering many pencil beams and robotic computerized 3D-dose planning systems instead of geometrically shaped single or two-dimensional field techniques and a low energy X-ray beam. Moreover, SHRT can be used as radical therapy or as a palliative treatment in the case of single or multiple distant metastases irradiated during a single set-up session. However, SHRT has one important limitation – it can only be used in the case of small and well-defined lesions.

This impressive progress in the use of radiation as one of the cancer treatment modalities provokes another important question: did all these achievements result in an increase of permanent curability of cancer patients, at least those with head and neck malignant tumors?

End-points of RT effectiveness

Since radiotherapy has been also used as a local treatment of malignant or some benign tumors or localized distant metastases, local tumor control (LTC) has been widely accepted.

That is why it is used as an appropriate end-point with a 5-year follow-up, at least for head and neck cancer, because about 80% of local recurrences occur within the first 3 years of completing the irradiation. However, when some cases are lost from observation and their follow-up is shorter than 5-years, then the actuarial LTC is limited, assuming the risk of recurrence which may occur if the follow-up lasts 5 years. The estimated date of an average limited LTC should therefore be interpreted with great caution because such averages might be underestimated.

Sometimes, LTC is erroneously identified with tumor cure probability (TCP), so it is misinterpreted as an indicator of tumor or even a patient's curability, which in fact is not. The TCP is only a preliminary predictor of local eradiation of the tumor by the RT and individually estimated based on the tumor origin, type, stage (in fact a tumor volume rather than a stage), and the planned dose fractionation. The TCP is estimated based on radiobiological principles, but it is very often untrue and thus disappointing. If the dose is heterogeneously distributed within the tumor volume, and, for example, 50% of the planned dose is delivered to only 1% of the tumor (usually invisible on a tumor volume histogram [DVH]), then it completely ruins the predicted TCP, and its real value decreases close to zero. Therefore, the TCP has nothing to do with a patient's curability by RT.

Complete tumor regression (CR) is definitely unsuitable for an evaluation of RT effectiveness, although there are some suggestions that the CR might be a prerequisite for the LTC, but it rarely happens. One may believe that the CR is the clinical effect of radiation cell kill, but it is not, because it only indicates how fast and effectively dead cancer cells are removed out of the tumor mass by immunological and cellular homeostatic defensive processes.

Disease-free-survival (DFS) is a proper and representative end-point which is close to the chance of the permanent patient's curability, because it represents the LTC without local recurrence and/or distant metastases. However, real DFS which is the absolute number of patients who survived the outlined follow-up, must be distinguished from the censored DFS, for the same reasons as a real *vs.* actuarial LTC. The more cases are censored the lower reliability of the estimates. The 5-year DFS seems a reasonable time-limit for the H&N cancer, but for some other tumors (e.g. breast, lung cancers), this period is too short, and sometimes even 10 years are not enough.

Overall survival (OS) is usually reported as an additional end-point, however its validity in relation to permanent patient's curability remains uncertain since it does not inform how many patients are permanently cured and how many live with local recurrence and/or distant metastases.

LTC, DFS, OS results in the last four decades of RT

The present survey is the review of a large variety of retrospective prospective studies and clinical randomized trials, whose results were published in the literature between 1970 and 2010. Many studies reported incomplete results. The present review includes only complete rates of well documented three end-points, which are the LTC, DFS and the OS, although not all three end-points were reported in each study [10, 17, 23–35]. Furthermore, only studies on radiotherapy alone or as a primary treatment or sometimes combined with sequential or concurrent chemotherapy were selected. Four decades of treatment have been analyzed, and therefore the respective number of end-points differ. Altogether, 341 rates of the LTC, DFS and OS have been selected for the present analyses (tab. I). The rate of LTCs reported up to 1970 are lower than LTC rates in the following decades. In the remaining three decades, the LTC, DFS and OS rates did not differ very much. The LTC, DFS and OS were estimated for an overall number of 21,058 patients treated by RT using one of the four different dose fractionation schedules (tab. II). All the data are subdivided into two groups, i.e. tumors in the early stage T1–2N0M0 and advanced tumors in stage T2–4N+M0. Altered *vs.* conventional dose fractionations were used in the randomized trials and the number of patients recruited to each arm of these studies was more or less the same. Therefore, the overall number of patients treated with conventional fractionation was the largest and it includes 10,209 cases (48%).

Figure 2 illustrates the distribution of dots representing the LTC, DFS and OS rates documented in the studies selected for the present review. This figure shows a wide spread of black dots representing the 5-year LTC and DFS of patients with locally advanced head and neck cancer reported during 1980–2010, although its ranges were relatively narrow, not substantially changed over the last 30–40 years. It should be emphasized that during that extended period, tremendous high-tech progress in linacs and its tools and computerized 3D--dose planning systems have taken place; yet it has not really

Table I. Number of studies analyzing three RT end-points recruited to the present survey

End point	1970–1975	1980–1985	1990–1995	≥2010	Overall
local tumor control		32	40	36	108
disease-free-survival	6	37	35	37	115
overall survival	8	35	37	38	118
total	14	104	112	111	

Table II. Number of patients included in the selected studies presented in table I

Radiotherapy schedules	Number of patients	Percentage of patients
conventional	2638	12
altered *vs.* conventional	15,142	72
SHRT	1863	9
chemoradiation	1415	7
total	21,058	100

SHRT – stereotactic hypofractionated multidimensional

improved LTC and DFS results, with average rates invariably oscillating around 40–45%. Even the use of altered dose fractionation did not change these highly unsatisfactory, average rates of LTC and DFS [24, 25]. Promising results have been offered by concurrent chemoradiation which increased average LTC and DFS by 10–15%. There is a marked increase in LTC and DFS for patients with early stages (T1–2N0M0) of head and neck cancer to an average level of 80–≥90%, and also when the SHRS has been used. By contrast to the LTC and DFS end-points, OS significantly increased from about 40–45% in the 80s to >70% in the 2000s. The higher rates and prolonged OS over these 30 years do not necessarily suggest a benefit of RT but rather a gradual progression of the disease from local to chronic.

Comments

The curability of cancer patients means that an appropriate therapy (radiotherapy alone or combined modalities) will permanently and irreversibly eradicate all clonogenic cancer cells. Theoretically it should result in a 100% permanent cure rate. For radiotherapy (also for other therapeutic modalities in oncology) this might be an illusion because of the random nature of radiation cell killing. Tumor stem cells are defined as clonogenic or colony forming cells, which may constitute only a small proportion of all tumor cells [36]. If only one stem cell survives irradiation, then it will be able to reconstruct the primary tumor as a local recurrence, although their genotype and phenotype may substantially differ from that in the primary tumor. Therefore, the key point of radiotherapy is to eradicate the last cancer stem cell, to ensure the tumor never regrows, but this is a theory only, and, moreover, it is impossible to recognize tumor stem cells in situ, and to establish their number and localization. Therefore, regarding a patient's curability, when estimating the LTC and DFS, the word "probability" instead of "certainty" is used.

Analyzing the results presented in the figure 2, two major questions arise. First, what is the reason for the small wide spread of dots representing the LTC, DFS and the OS, despite the outstanding technological and computerized 3D-RT planning advances during the last three decades; secondly, why during that period, did the RT efficacy represented by the LTC and DFS rates not increase? It seems that there are at least three important reasons. First of all, in clinical radiotherapy for H&N cancer clinical data, not only that recruited the present study, look like a "fruit basket". To a single study or two-three arms of the randomized trials were usually recruited H&N tumors with various sites and wide range stages (T2–4N+M0) [25, 26, 37]. Therefore, the range of initial tumor volumes (and respective initial number of cancer cells as well) was even wider. For such a diversity of parameters, a single and same 3D-dose fractionation was used within each arm of the study. The main aim was to estimate the most effective dose which would produce a significant increase in LTC and DFS. The use of the same dose fractionation for T2N0M0 as for T4N0M0 to achieve the highest therapeutic benefit is in fact ridiculous in the light of all radiobiological principles. Some years ago, L. Peters suggested that it is like searching for a single "Holy Grail", which could be

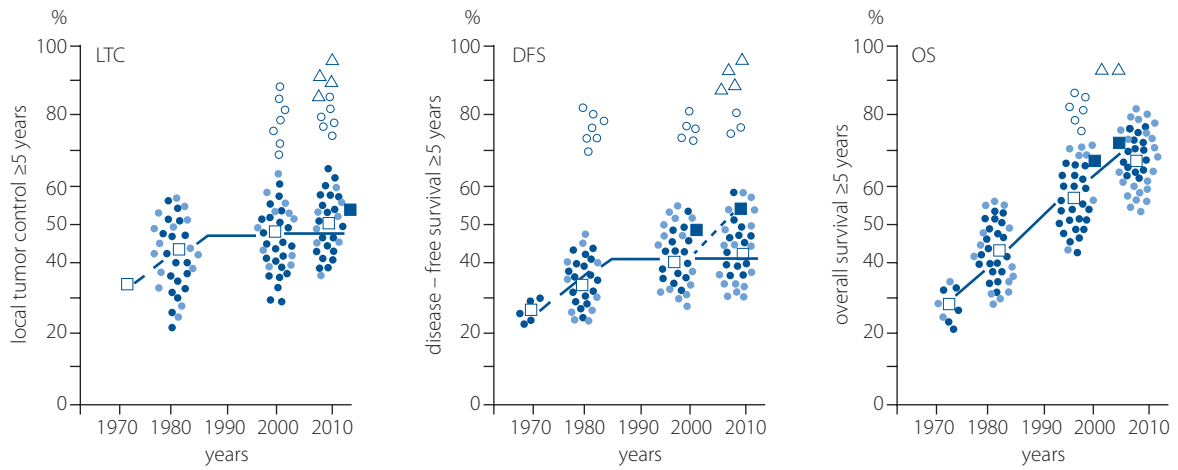

Figure 2. Distribution of the 5-year LTC, DFS and OS rates of (dost) during four decades of radiotherapy documented by the results of studical recruited to the present survey □ – average rates of the respective end-points for advanced H&N cancers; ■ – average rates representing concurrent chemo-radiation; open circles – early staged H&N cancers; △ – results of the SHRS

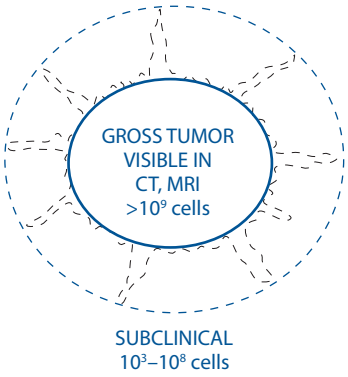

Figure 3. Schematic tumor volume (gross mass) with subclinical microscopic irregular cancer cell deposits

compared with a blind man looking for a needle in a haystack. The effect of the mixture of tumors in early and advanced stages is shown as a theoretical example in figure 3.

From a practical point of view, if the total dose of 70 Gy in 35 fractions is used to irradiate T1N0M0 H&N cancer, which contains about 10^9 clonogenic cancer cells then on average 0.1 cell/tumor should theoretically survive. It means that in a group of 100 such tumors, in 90 of them all the cells will die and in the remaining 10 tumors, 2, 4, 8 or more cells will survive, which gives on average 0.1 cell/tumors. Therefore, tumor cure probability (TCP = $e^{-0.1}$) will reach a level of 90%, which usually happens in RT practice. However, if the same dose is used to irradiate T3N0M0 tumor with 10^{11} clonogenic cells, then an average survival would be 1 cell/tumor, which as a consequence gives TCP of e^{-1} = 37%, what also happens? This is not a theory but a real every day situation in radiotherapy.

One important point of view articulated 75 years ago in 1949 by Paterson [1], and 50 years later by Suit [38], is that a local success, important for patients, is to be free of local problems, but it does not affect the likelihood of the patient's curability.

An increase in the DFS seems to be realistic by effectively augmenting the LTC. Already Paterson in his textbook of radiotherapy published in 1949 (the first textbook in the world) strongly emphasized that "optimal tumor dose (TCD is actual term) must be assessed in terms of dose related to time, not as a dose alone. The dose/day of treatment is important from the beginning, because a low initial rate cannot be compensate by a high rate later, or vice versa. A most often forgotten corollary is that the treatment planned must be completed in the shortest time possible". It should lower a risk of local recurrences and/or distant metastases (the last failure type is not a key-problem in the case of the H&N squamous cell carcinomas, may be except nasopharyngeal cancer). It may seem surprising (fig. 2) that average rates of the LTC and DFS for advanced tumors have remained at a similar level during the last 30 years. One plausible explanation could be that LTC rates shortly after completing RT were much higher, and they decreased during the follow-up, as the result of local recurrences. Finally, averages of both end-points reached similar levels at the 5-year follow-up. At first glance, a relatively wide spread of data dots representing the LTC and DFS rates may suggest differences in tumor radiosensitivity, but it is unrealistic to accept such wide variations in squamous cell carcinomas which are the subject of the present review. It could rather be the results of the pronounced variability in the initial tumor volume and the respective number of cancer cells (not TNM), which received a suboptimal radiation dosage. Falling into two major categories of H&N cancers, the LTC for tumors in the early stage treated adequately is very high, whereas for advanced tumors the LTC is usually low, and therefore the average rate is unexpectedly more or less moderate. In the present analysis we decided to separate these two categories.

High curability is a fundamental goal of radical RT, which can be attempted when the whole area containing cancer cells is covered homogenously by respectively optimal dose delivered in the shortest overall time possible. Moreover, an important point is that cancer should be effectively controlled at the first attempt, because there is seldom a second chance. And this is the next important problem.

Generally, cancers usually have an irregular shape (except capsular or cystic tumors, very rare in the H&N) with the spread of subclinical cellular deposits beyond the bounds of the gross tumor mass (fig. 3). Gross mass is the only visible part of the tumor on the CT, MRI scans, and therefore the real tumor bounds cannot be precisely defined, since subclinical spread of tumor cell deposits are beyond the resolution of the CT or MRI and it is unable to determine the exact extent of the growing tumor. Spread of cellular deposits beyond the gross tumor mass is a major attribute of advanced rather than "early" tumors.

Currently, the aim of 3D conformal RT planning is to tailor irregularly shaped radiation beams within the CTV and PTV margins, and focus on the gross tumor mass, and with the dose gradient beyond, to spare the surrounding [fig. 3] normal tissue. Therefore, there is a risk of missing microscopic deposits of cancer cells aside individual volume. Regardless of that risk, collimator leaf(s) may sometimes cover even a very small part of the tumor volume (overconformality). Both events are a potential source of local recurrence of the tumor. If 10^3–10^6 clonogenic cancer cells were missed (even 1 stem cell is enough) beyond the irradiated volume, then local recurrence will likely occur clinically during 6–12 months after completing the treatment. To minimize that risk, the planned dose-volume-histograms (DVH) must be very carefully analyzed. It has to be emphasized that purely physical dose distributions might be misleading, and therefore the physical DVH should be converted into biologically normalized DVHs, where each pixel of dose becomes equivalent if it would be given in 2.0 Gy/fractions. Such a simple procedure discloses overdosage or underdosage

subregions of the whole tumor volume. It is a pity that such checking is often ignored in daily RT practice, and therefore, it could partially contribute in some way to the unsatisfactory average rates of LTC and DFS, shown in figure 2.

Dose cold and hot spots (the second one in the gross tumor volume can be ignored) are the third major problem, especially for heterogeneous dose distribution within the irradiated area. The UICC recommends using the D_{95} as a reference parameter and it was acceptable for 2D dose planning homogenously distributed within the irradiated volume. When the 2D procedure was replaced by precise and highly sophisticated 3D–4D dose planning techniques, already more than 10 years ago, Jack Fowler strongly emphasized that D_{95} should, without doubt, be replaced by D_{100} as a reference factor, however the D_{95} still remains in daily practice. If preliminarily predicted TCP is 90% and dose planning is tailored to such prediction, that if even a small tumor subvolume will receive a few percent lower dose (cold spot), then in such an underdosed subvolume on average 1.0 instead of 0.1 cancer cell will survive, and therefore the TCP for that subvolume will be substantially lowered (TCP = e^{-1} = 0.37), and collorary overall LTC will lower to only 33% (0.90 x 0.37).

Withers [22] and Suit [38] pointed out that "the essential art of treatment planning is choosing where and how much of extra-tumoural radiation shall go". However, this does not necessarily seem to be true after all, since once a tumor cold spot is underdosed, it will definitely ruin the expected high LTC, and any extra boost dose delivered thereafter will not neutralize such negative effect. Therefore this moves us to the beginning, that precise 3D-dose planning with the removal of any existing dose cold spots is a key point in achieving the LTC and DFS as high as predicted.

A final comment as regards overall survival (OS) in the present review shows an increasing tendency through the last 30 year period. The OS is not a proper and adequate end-point for an assessment of the patient's permanent curability, although it is often used as an argument to express improvements of the efficacy of oncologic therapy as a whole. In the present review relatively moderate 5-year LTC and DFS of 45–50% compared with much higher average the OS may likely be interpreted as the gradual progress of a local cancer disease into its chronic phase (in about 20–25% in the present review), and the higher OS with prolonged survival can be a result of effective palliative therapy. SHRS has been found as a highly effective RT, not only radical but also local palliative therapy as well [19, 20]. Analyzing the OS as an end-point for prolonged survival, there is relatively small number of studies focused on the quality of life and what kind of price is paid for prolonged life. It does not look very optimistic. According to List and Bilir [39], about more than 50% of patients have difficulties in eating and swallowing, a decreased sense of taste, dry mouth (95%) and 30–35% reported sticky saliva, pain, unsatisfied appearance, which may recover is less than 35% of patients. This is the price which patients with a chronic phase of H&N cancer may pay for prolonged survival, in other tumor types and origins as well.

To sum up, it is a pity that RT efficacy for locally advanced H&N cancer has not changed a lot during the last 3 decades and it still does not look overly optimistic, but it is not all bad news. Tumors in the early stage usually have well defined bounds as microscopic deposits of cancer cells have not had enough time to develop yet and therefore have not spread out of the tumor bounds. Radiation beams are precisely tailored to cover homogenously whole PTV to eliminate overconformality, or dose cold spots. Therefore, the likelihood of a high LTC and DFS (~80–90%) by RT alone is not surprising. On the contrary, many studies including trials on various 3D-techniques and altered dose fractionation [15, 21, 23, 26, 28, 29] have convincingly shown that the effectiveness of RT alone for advanced H&N cancers is limited and generally disappointing. Ultimate proof of that comes from the four-arm RTOG-9003 trial [24]. Delivery of a total dose in the range of 67.2–81.6 Gy using altered fractionation to irradiate advanced H&N cancers resulted in similar LTC of 40–45%, in each arm of this trial. This became a strong argument for replacing RT alone by combined therapeutic strategy, which includes RT. Concurrent chemoradiation has been an attractive solution, although meta-analysis [26] showed a rather low (4%) average benefit of local tumor control. Combined therapy including various sequences of surgery, radiation and chemotherapy has been enriched by genomic, proteomic-molecular identifiers and modifiers (fig. 4), becoming promising options to improve cancer patient's permanent curability. The point to be emphasized is the advertisement of a "quantum leap" in the improvement of the efficacy using 3D-IMRT in the local treatment of various tumor sites including the use of respiratory gating in the case of lung cancer. Glatstein [40, 41] pointed out that many investigators admit they are still uncertain, but suspect that some improvement could be expected. An objective evaluation of the benefits of IMRT has never been done and it still remains an open question. It is often suggested that high-tech RT has a high success rate but it is unclear as to what that success refers to, i.e., a permanent cure or local control only. Moreover about 80% patients are treated using RT beyond clinical trials.

Irrespective, of many uncertainties [44, 45], the "evidence based" RT is strongly forced and recommended as an obligatory guide and instruction for the RT planning and delivery based on the trial's results. However, throughout all these efforts, spanning 30 years, of trying to improve RT efficacy, the recruitment of various, different tumor sites and sizes (although all being squamous cell cancers) to each arm of the trials to test one or two different RT schedules is an antimony of individual therapy, and in fact it fails. Some trials evaluating molecular agents combined with RT are restricted to the conclusion that the tested regimens are safe

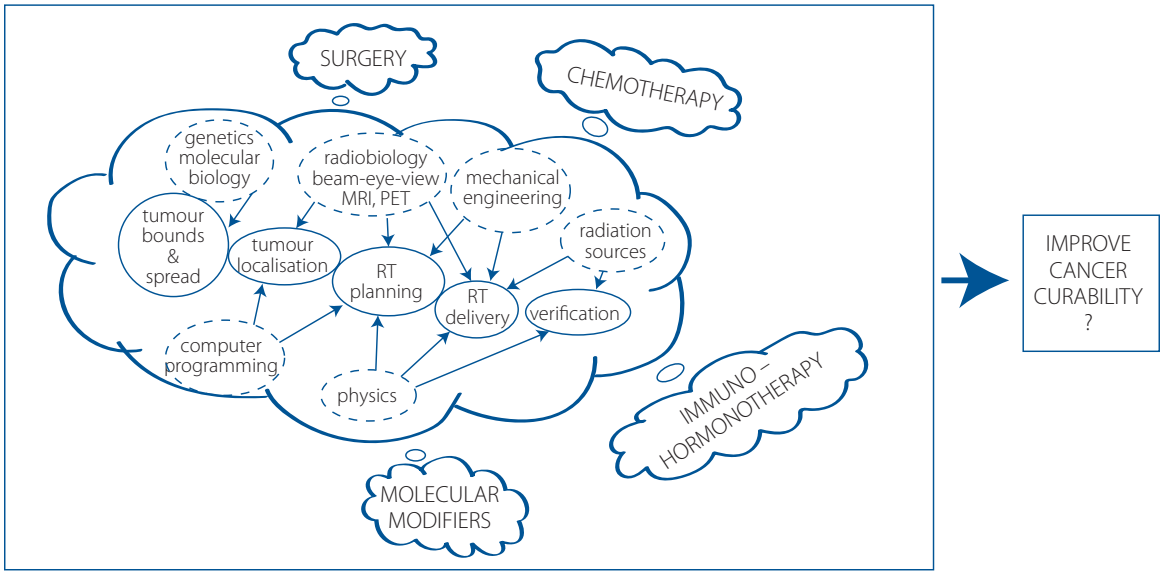

Figure 4. Scheme of the elements of multimodality combined treatment: strategy as an instrument for improvement cancer curability

Table III. Local tumor control depending on ratio of early *vs.* advanced stage cancer treated by RT

Current and expected rate of early *vs.* advanced cases		Early	Advanced	Early and advanced
current rate	no. cases	40	60	100
	average LTC	80%	20%	44%
	no. with LTC	32	12	44
expected rate	no. cases	70	30	100
	average LTC	80%	20%	62%
	no. with LTC	56	6	62

LTC – local tumor control

and feasible – not one word regarding its efficacy is mentioned. Thus, it seems reasonable and reliable that "evidence based" cancer therapy (results are often biased and are not reliable facts) might be replaced in favor of "personalized combined therapy", individually tailored to each single cancer patient. But this seems to be a promising future only, which we believe in or not. In conclusion, the only reasonable solution at the present moment, is to intensify all efforts to change the unsatisfactory ratio of early versus advanced tumors from 4:6 to 7:3, in favor of early stage tumors (tab. III B). Detection of cancers in the early stage of disease needs intensive and convincing efforts to increase access to early and fast diagnostics to effectively increase public awareness that till now early detection of cancer is reasonable solution to achieve the highest permanent curability for the patient.

Article information and declarations

Conflict of interest

None declared

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