Has innovations in radiotherapy for head and neck cancer improved patients curability?

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DOI: 10.5603/njo.95700
Article type: Review paper
Submitted: 2023-05-24
Accepted: 2023-07-18
Published online: 2023-08-21


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Has innovations in radiotherapy for head and neck cancer improved patients curability?

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In the era of distinct technological innovations in radiotherapy, clinically important question arises has the increase of the RT effectiveness been achieved due to these innovations, at least in case of the head and neck (H&N) cancers. To answer to this question 133 studies published in the literature, including 21 058 patients with H&N cancer treated in the period a 1970-2010 years were selected to the present survey. Three end-points, e.g. 5-year local tumour control (LTC), disease-free survival (DFS) and overall survival (OS) and its averages have been evaluated in the consecutive decades of time. 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 the LTC and an DFS were also constant, but much lower (40-45%) than expected. The OS has an increasing tendency from 45–50% in 1980 to more than 70% in 2010. It may suggest that during the 5-year follow-up some rate (~20%) of advanced tumours gradually progressed from local to chronic disease. Various technical and clinical problems influencing the results of the present review are discussed in details. Some uncertainties and doubts regarding the RT trials may suggest that “evidence based” recommendations are not a good ambassador enough, and in the era of combined treatment modalities it may seem reasonably to replace it by “individually personalized combined
therapy”. However, nowadays the only plausible solution to improve H&N curability is to intensify all efforts to detect H&N cancer in a very early stage of disease and to increase various activities to convince people to participate in regular prophylactic examinations.

**Key words:** H&N cancers, LTC, DFS, OS end-points, early cancer diagnosis, permanent curability

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**Technological revolution and innovations**

Era of the orthovoltage radiotherapy (RT) and the Ralston Paterson’s “school of radiation dose delivery” [1] lasted over 60 years from the beginning of this treatment modality for the cancer patients. 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 tumour (fig. 1), and dose distribution was calculated based on diagrams of the percentage depth isodoses.

During the 70s, cobalt units were consistently replaced by the high-tech linear accelerators (Linacs), offering wide range MV energy (5 – >20 MV) photon and electron beams. Instead of the Paterson’ principles, the Fletcher’s rules based on radiobiological fundamentals, has been universally accepted [2]. Linacs were gradually enriched with multileaf collimators (MLC), cone-beam CTs, real-time tumour tracking, fusion of the CT and Linacs (tomotherapy). Corollary to these technological innovations, the RT planning has begun to use precise 3D-conformal IMRT, IGRT, IART, respiratory gating RT, biologically targeted IMRT [3–14], which were defined by Coleman et al. [12] as the SMART radiotherapy. Irregular beam’s shapes have allowed to taylor radiation dose being focused on the tumour and its margins, with a sharp decrease beyond this area (fig. 1). However, daily clinical practice has shown this comprehensive and powerful solution is in fact the Damocles two-edged sword. On the one edge conformal techniques offer substantial decrease in the dose deposited in the surrounding normal tissues, and therefore reduce the risk of serious late complications. The opposite edge leads however to the risk of cold spot(s), even small one, in the tumour volume, due to dose overconformality within the tumour, which could likely lower preliminary predicted probability of local tumour control [14].
Such technological and systemic revolution [3–14] in the three-dimentional RT has opened the door for various altered dose fractionation schedules used alone or combined with other therapeutic modalities as (surgery, chemotherapy) [12, 15–17]. Moreover, proton and boron therapy came to the RT market, but the facilities and its installation are extremely expensive and its practical use is still limited. The next interesting offer with growing attractiveness has been the stereotactic hypofractionated radiotherapy (radiosurgery, SHRT, SHRS) [18–20]. Although its principles was already defined in 1948 by Takahaschi [8], the SHRT has widely been used since 2000, mainly due to special modifications of the linacs (VMAT) and new robotic CyberKnife. Key-principle of this method is the use of many (even more than 100) pencil beams focused on the tumour, with sharp down dose gradient beyond its bounds (fig. 1). The SHRT is an example of “round game” in radiotherapy, that means the return of the RT to its roots, when in the 1900-ties, single or a few large dose fractions were used. This method was however pretty fast definitely abandoned because of very high incidence of lethal late complications. And after more than 100 years, it came back to the RT market, offering many pencil beams and robotic computerized 3D- dose planning system instead of geometrically shaped single or two- 2D- field techniques and low energy X-ray beam. Moreover the SHRT can be used as radical therapy or as a palliation in the case of a single or multiple distant metastases irradiated during a single set-up session. However, the SHRT has one but important limitation – it can be used in case of small well-defined lesions only.

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

End-points of the RT effectiveness

Since the radiotherapy has been used as a local treatment of malignant or some benign tumours, or localized distant metastases as well, LOCAL TUMOUR CONTROL (LTC) has been widely accepted and used as an appropriate end-point with 5-year follow-up, at least for head and neck cancer, because about 80% of local recurrences occur within the first 3 years
after completing the irradiation. However, when some cases are lost from observation and their follow-up is shorter than 5-years, then the actuarial LT is censored, assuming the risk of recurrence which may occur if the follow-up would last 5 years. Estimates of an average censored LTC should therefore be interpreted with a great caution because such averages might be underestimated.

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

Complete tumour regression (CR) is definitely unsuitable for evaluation of the RT effectiveness, although there are some suggestions that the CR might be a prerequisite for the LTC, but it rarely happens. One may indulge with illusion 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 tumour mass by immunological, and cellular homeostatic defensive processes.

Disease-free-survival (DFS) is likely 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 an absolute number of patients who survived the outlined follow-up, must be distinguished from the censored DFS, for the same reasons as an real vs. actuarial LTC. The more cases are censored the lowest reliability of the estimates. The 5-year DFS seems reasonable time-limit for the H&N cancer, but for some other tumours (e.g. breast, lung cancers) 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 the RT**

Present survey is the review a large variety of retrospective prospective studies and clinical randomized trials, which results were published in the literature in various periods between 1970 and 2010. Many studies reported incomplete results. One the contrary, 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, the studies on radiotherapy alone or as a primary treatment or sometimes combined with sequential or concurrent chemotherapy were only selected. Four decades of time have been analyzed, and therefore the respective number of the end-points differ. All together 341 rates of the LTC, DFS, OS are selected to the present analyses (tab.I). The number of the LTCs reported up to 1970 are the lowest one of the LTC rates in the following decades. In the remaining three decades, the LTC, DFS, OS rates did not differ very much. The LTC, DFS, and OS were estimated for overall number of 21 057 patients treated by RT using one of the four different dose fractionation schedules (tab. II). All gathered data are subdivided into two groups, i.e. tumours in the early stage T_{1-2}N_{0}M_{0} and advanced tumours in stage T_{2-4}N_{+}M_{0}. 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 overall number of patients treated with conventional fractionation was the largest one and it includes 10 209 cases (48%).

Figure 2 illustrates distribution of dots representing the LTC, DFS and OS rates documented in the studies selected to 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, and did not substantially changed during the last 30–40 years. It should be emphasized that during that long period, tremendous high-tech progress in the linacs, its tools and computerized 3D-
dose planning systems has occurred but it has not really improved the LTC and DFS results, which average rates invariably oscillate around 40–45%. Even the use of altered dose fractionation did not change this unsatisfied average rates of the LTC and DFS [24, 25]. Promising results has been offered by concurrent chemoradiation which has increase an average LTC and DFS by 10–15%. There is distinguished increase in the LTC and DFS for patients with early stage (T1–2, N0, M0) of head and neck cancer to an average level of 80 – ≥90%, and also when the SHRS has been used. By the contrast to the LTC and DFS end-points, the OS significantly increased from about 40–45% in the 80s to >70% in the 2000s. Higher rates and prolonged OS during these at least 30 years not necessarily suggest a benefit of the RT but rather gradual progression of local into chronic disease.

Comments..., comments

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

Analyzing results on the figure 2, two major questions arise. First, what is the reason of a small wide spread of dots representing the LTC, DFS and the OS, in spite of outstanding technological and computerized 3D-RT planning advances during the last three decades, and the second one, why during that period, the RT efficacy represented by the LTC and DFS rates did not increase. It seems, 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 tumours with various and wide range stages \((T_{2-4}N_{0,1}M_{0})\) [25, 26, 37]. Therefore the range of initial tumour volumes, and (respective initial number of cancer cells as well) was even wider. For such diversity of parameters, a single and the same 3D- dose fractionation was used within each arm of the study. Major aim was to estimate the most effective dose which would produce significant increase in the LTC and DFS. The use of the same dose fractionation for \(T_{2}N_{0}M_{0}\) as for \(T_{4}N_{0}M_{0}\) to achieve the highest therapeutic benefit is in fact ridiculous in the light of all radiobiological principles. Couple years ago, L. Peters suggested that it is like a search of a single “Holy Grail”, which could be compared with a blind man looking for a candle light. An effect of the mixture of tumours in early and advanced is shown as a theoretical example in figure 3A.

From the practical point of view, if total dose of 70 Gy in 35 fractions is used to irradiate \(T_{1}N_{0}M_{0}\) H&N cancer, which contains about \(10^9\) clonogenic cancer cells then on average 0.1 cell/tumour should theoretically survive. It means that in the group of 100 such tumours, in the 90 of them all cell will die and in the remaining 10 tumours will survive 2, 4, 8 or more cells, which gives on average 0.1 cell/tumours. Therefore tumour cure probability (TCP = \(e^{-0.1}\)) will reach the level of 90%, what usually happens in the RT practice. However, if the same dose will be used to irradiate \(T_{3}N_{0}M_{0}\) tumour with \(10^{11}\) clonogenic cells, then an average survival would be 1 cell/tumour, which as a consequence gives TCP of \(e^{-1} = 37\%\), what also happens? This is not theory but real daily 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 problem, but it does not affect the likelihood of patient’s curability.

An increase in the DFS seems to be realistic by effective augmenting the LTC. Already Paterson in his Textbook of radiotherapy edited in 1949 (the first textbook in the world) strongly emphasized that optimal tumour 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 low initial rate cannot be compensate by a high rate later, or vice versa. Most often forgotten corollary is that treatment one planned must be completed in the shorter time possible. It should lower a risk of local recurrences and/or distant
metastases (the last failure type is not a key-problem in 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 tumours have remained at the similar level during the last 30 years. One of plausible explanation could be that the LTC rates shortly after completing the RT were much higher, and they decreased during the follow-up, as the result of local recurrences. Finally, averages of both end-point reached similar level at 5-year follow-up. At the first glance, relatively wide spread of data dots representing the LTC and DFS rates may suggest differences in the tumour radiosensitivity, but it is unrealistic to accept such wide variations in squamous cell carcinomas which are the object of the present review. It could rather be the results of the pronounced variability in the initial tumour volume and the respective number of cancer cells (not TNM), which received suboptimal radiation dosage. Falling into two major categories of the H&N cancers, the LTC for tumours in the early stage treated adequately is very high, whereas for advanced tumours the LTC is usually low, and therefore average rate is unexpectedly more or less moderate. In the present analysis we decided to separate these two categories, and the reason will be explained later.

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

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

Currently, the aim of 3D conformal RT planning is to taylor irregularly shaped radiation beams, within the CTV and PTV margins, and focused on a gross tumour mass, and with the dose gradient beyond, to spare 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 very small part of tumour volume (overconformality). Both events are potential source of local recurrence of the tumour. If there would be \(10^3-10^6\) clonogenic cancer cells missed (even 1 stem cell is enough) beyond the irradiated volume, then local recurrence will likely occur clinically during 6–12 month after completing the treatment. To minimize that risk the planned dose-volume-histograms (DVH) must be very carefully analysed. 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, which each pixel of dose becomes equivalent if it would be given in 2.0 Gy/fractions. Such simple procedure discloses overdosage or underdosage subregions of the whole tumour volume. It is a pity that such checking is often ignored in the daily RT practice, and therefore, it may at least partially contribute to unsatisfied average rates of the LTC and DFS, shown in figure 2.

Dose cold and hot spots (the second one in the gross tumour volume can be ignored) are the third major problem, especially for heterogeneous dose distribution within irradiated area. The UICC recommends to use the \(D_{95}\) as a reference parameter and it was acceptable for 2D planning the dose homogenously distributed within irradiated volume. When 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 be, with no doubt, replaced by \(D_{100}\) as a reference factor, however the \(D_{95}\) still remains in the daily practice. If preliminarily predicted TCP is 90% and dose planning is taylored to such prediction, that if even a small tumour subvolume will receive a few percent lower dose (cold spot), then in such underdosed subvolume will survive on average 1.0 instead of 0.1 cancer cell, 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% \((0.90 \times 0.37)\).

Withers [22] and Suit [38] pointed out that the essential art of the treatment planning is choosing where and how much of extra-tumoural radiation shall go. Finally, this does not necessarily seems to be true after all, since once tumour cold spot would be underdosed, then 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 removing of any existing dose cold spots is a key point to achieve the LTC and DFS as high as predicted.

Final comment regards overall survival (OS) which in the present review shows increasing tendency through the last 30 year period. The OS is not a proper and adequate end-point for assessment patient’s permanent curability, although is often used as an argument to express improvement 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 gradual progress local cancer disease into chronic phase (in about 20–25% in the present review), and the higher OS with prolonged survival can be result of effective palliative therapy. SHRS has been found as 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 the price is payed for the 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, 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 a price which patients with chronic phase of H&N cancer may pay for prolonged survival, in other tumour types and origins as well.

To sum up, it’s a pity that the RT efficacy for locally advanced H&N cancer did not change a lot during the last 3 decades and it don’t look very sunny, but it is not entirely in the shadow. Tumours in the early stage usually have well defined bounds and microscopic deposits of cancer cells did not have enough time to develop yet and therefore did not spread out of the tumour bounds. Radiation beams are precisely tailored to cover homogenously whole PTV to eliminate overconformality, or dose cold spots. Therefore, likelihood of a high LTC and DFS (~80–90%) by the RT alone is not be surprising. Quite the contrary, many studies including trials on various 3D-techniques and altered dose fractionation [15, 21, 23, 26, 28, 29] convincingly have shown that the effectiveness of the 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 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
the RT alone by combined therapeutic strategy, which includes RT as a part of that. Concurrent chemoradiation has occurred an attractive solution, although meta-analysis [26] showed rather low (4%) average benefit of local tumour control. Combined therapy including various sequences of surgery, radiation and chemotherapy has been enriched by genomic, proteomic-molecular identifiers and modifiers (fig. 4) and has become promising options to improve cancer patient’s permanent curability. The point to be emphasized is advertisement of a "quantum leap" in the improvement of the efficacy using 3D-IMRT in the local treatment of various tumour sites including the use respiratory gating in case of lung cancer. Glatstein [40, 41] pointed out that many investigators admit they are not really sure, but simply suspect that some improvement can be expected. Objective evaluation of the IMRT benefit has ever been done and it still remains an open question. This is often suggested the high-tech RT claims high success but it is unclear to what that success refers – to permanent cure or to local control only. Moreover about 80% patients are treated using RT beyond clinical trials.

Nevertheless of many uncertainties [44, 45], the "evidence based" RT is forced as an obligatory guide and recommended as an obligatory guide and instruction for the RT planning and delivery based on the trial's results. However, throughout all these 30 year efforts trying to improve the RT efficacy, the recruitment of various, different tumour 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 the RT are restricted oneself to the conclusion that the tested regimens are safe and feasible – no even one word regarding its efficacy. Thus, it seems reasonable and reliable that "evidence based" cancer therapy (results are often biased and are not reliable facts) might be replaced in favour of “personalized combined therapy”, individually tailored to each singe 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 unsatisfied ratio of early versus advanced tumours from ratio 4:6 to a ratio 7:3, in favour of early stage tumours (tab. III B). Detection of cancers in the early stage of disease needs an intensive and convincing efforts to increase access to early and fast diagnostics and to effectively popularize and enlighten that early detection of the cancer can quarantinee the highest permanent patient's curability.
Conflict of interest: none declared

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Received: 24 May 2023
Accepted: 18 Jul 2023

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fractionated radiotherapy in head and neck squamous cell carcinoma (HNSCC): final


Figure 1. Schemes of three different techniques used in radiotherapy during <1970 and ~1990 >2000 year with respective dose distribution within the tumour (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

Figure. Distribution of the 5-year LTC, DFS and OS rates of (dost) during four decades of
e 2. 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

Figur Schematic tumour volume (gross mass) with subclinical microscopic irregular
cancer cell deposits

Figur Scheme of the elements of multimodality combined treatment: strategy as an
instrument for improvement cancer curability
**Table** Number of studies (1970 – ≥2010) analyzing three RT end-points recruited to the present survey

<table>
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<tr>
<td></td>
<td>1985</td>
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<td>LTC</td>
<td>7</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>DFS</td>
<td>6</td>
<td>37</td>
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<td>8</td>
<td>35</td>
<td>37</td>
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| all       | 14   | 104       | 112   | 111   |

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

<table>
<thead>
<tr>
<th>Radiotherapy schedules</th>
<th>Number of patients</th>
<th>%</th>
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<tbody>
<tr>
<td>conventional altered vs. C</td>
<td>2638</td>
<td>12%</td>
</tr>
<tr>
<td>Conventional SHRS chemoradiation</td>
<td>15,142</td>
<td>72%</td>
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<tr>
<td></td>
<td>1863</td>
<td>9%</td>
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<td></td>
<td>1415</td>
<td>7%</td>
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<tr>
<td>all</td>
<td>21058</td>
<td>100%</td>
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Scheme of average and overall local tumour control depending on ratio of early vs. advanced staged cancer treated by the RT. A – still actual situation of the advantage and advanced tumours; B – expected change in favour of early staged tumours.

#### Early

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<td>20%</td>
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<tr>
<td>overall: no. LTC%</td>
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<td>44%</td>
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#### Advanced

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<th>B. no. cases:</th>
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<th>30</th>
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<tbody>
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<td>average LTC:</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>no. with LTC</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>overall: No. LTC%</td>
<td>62/100</td>
<td>62%</td>
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