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The dose no longer plays a paramount role in radiotherapy (oncology), but time apparently does

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Overall 80 clinical data sets (head and neck, breast, lung and prostate) have been selected from the literature (about 10,000 patients) to analyze and compare the importance of the total dose (D) *vs.* overall therapy time (OTT). There was no correlation between local tumor control (LTC) and dose used as a single parameter. On the contrary, for tumors (larynx and cervix cancer) treated with a constant $TCD_{50} \pm 5\%$, any extension of the ORT resulted in a significant decrease of the LTC by about 1.5–2% per each one day extension of the ORT. Dose intensity (DI) expressed by the number of gray per unit of time (day) strongly correlated with the LTC, which significantly increases when the DI becomes larger than 7 Gy/day. The results lead to a final conclusion that suggests inverse order of the planned treatment parameters, i.e. TIME plays the primary role in treatment and the DOSE (and its fractionation) is a consequence of the primary choice.

Key words: total dose, overall therapy time, dose intensity

Introduction

Over the past years, the final diagnosis of malignant solid tumors has been continuously widened by various prognostic and predictive parameters, including histological type, stage and localization, molecular, genetic, hormonal and kinetics factors or parameters. This has resulted in an increasing variety of tumor geno- and fenotypes, even within the same histological type, stage and localization.

The choice of a proper and optimal combined therapeutic strategy for a given tumor has become more and more individualized, but it may raise some doubts and uncertainties. This situation also applies to radiotherapy.

Through the last decades, new sophisticated and precise accelerators, techniques and dose fractionation schedules have entered the market and daily radiotherapy practice. Since the early years of radiotherapy, despite all these novel biological, clinical and technological options and solutions, the total dose invariably has remained of paramount importance and is still the first parameter chosen in the radiotherapy planning.

Is the TOTAL DOSE really the leading parameter and the most important factor which determines treatment efficacy (permanent local tumor control is not always equivalent to the patient's curability)? Is it proven with no doubts or is it only a unequivocally accepted paradigm or custom? The present review tries to answer this question.

Material and methods

Among many widely recognized studies on radiotherapy for various tumor types, four important cancers have been chosen i.e. head and neck [1–6, 24], breast [7–16], lung [18–21] and prostate [23–24]. It is obvious that such studies include various clinical factors and a variety of combined treatment strategies. Therefore, from numerous important papers published in leading journals, data sets were selected which comply with the following criteria:

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- radiotherapy was the primary or the only treatment modality,
- at least a 3-year local tumor control follow-up (in some data sets it was even 5- or 10-years, e.g. breast and prostate),
- all fractionation parameters and irradiation methods were reported in details,
- epithelial or adenocarcinomas only.

Altogether, 75 data sets (10,000 cases) were selected (tab. I), among which 15 were treated with conventional fractionation, 23 with altered, and 32 with stereotactic hypofractionated radiotherapy.

Even though the individual TNM stage was considered, the tumor data sets were arbitrarily subdivided into two groups: early and advanced. Fractionation schemes concerned conventional, altered (accelerated, hyperfractionated or hybrid) and stereotactic hypofractionated radiosurgery.

Table I. Data sets characteristic

Tumour	Fraction		
	conventional	altered	stereo hypofx
head and neck	'4	3	4
breast	3	5	8
lung (NSCLC)	5	3	'2
prostate	3	2	8
overall	15	23	32

The first step of the analysis was focused on the relationship between minimum 3-year local tumor control (LTC) and a given TOTAL DOSE only. In the next, the data sets have been used to estimate TCD_{50} values (total dose producing 50% LTC). Only cases which received such TCD_{50} doses were chosen, and at least the 3-year LTC rates were related to the overall radiotherapy time (ORT).

Finally, using fractionation parameters characterizing individual data sets, dose intensity (DI) values were calculating using the following simple formula: DI = TD/ORT [1], representing the number of g rays delivered in the unit of time (Gy/day).

Once again, the 3-year LTC were related to a given Gy/day values. This part of the analysis is important because it illustrates the biological/clinical power (LTC) of the delivered irradiation independently on the number and size of dose per fraction. For example, doses of 60 Gy in 30 fractions in 42 days, 70 Gy in 35 fractions in 49 days, and 80 Gy in 40 fractions given in 56 days characterize the same DI value of 1.43 Gy/day, whereas, i.e. 20 Gy given in 10 days the DI equals 2.0 Gy/day, compared with the DI of 10 Gy/day if 20 Gy is delivered in 2 days.

Results

Total dose

An analysis of the relationship between the total dose (Gy) and at least 3-year local tumor control (LTC) for four different cancer localizations (fig. 1A–D) did not reveal any correlation

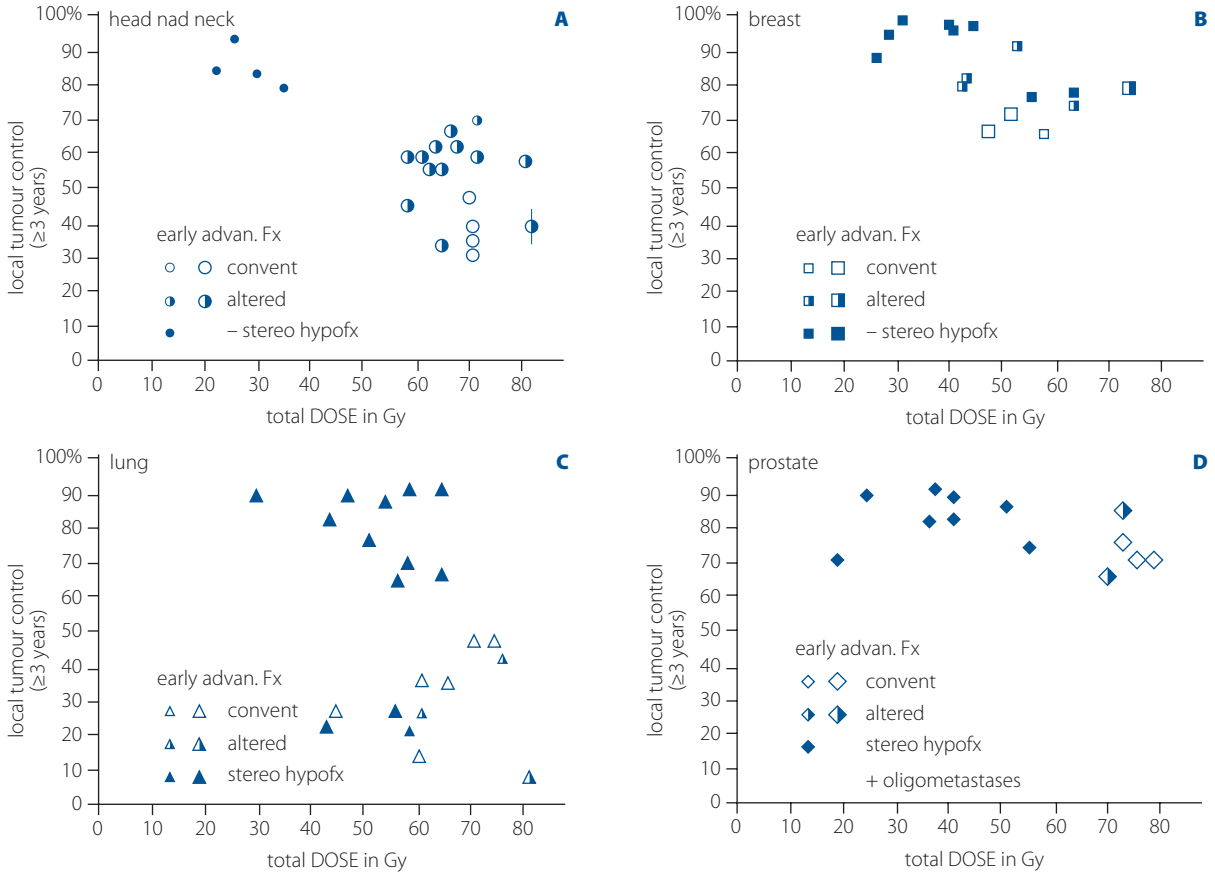

Figure 1. Local tumour control – total relationship (A–D) (A – head and neck, B – breast, C – lung, D – prostate)

of the LTC with total doses – irrespective of the dose fractionation. However, high or even very high LTC occurred when stereotactic hypofractionated radiosurgery (SHRS) was used, although this is characterized by much lower total physical doses. It mainly concerns prostate cancer (fig. 1D) but not necessarily the lung cancer data sets (fig. 1C), because the SHRS produced low (<50%) for some cases or very high LTC for others. Subsequently, it is difficult to accept total dose as a primary and major or even meaningful single parameter determining the final efficacy of fractionated radiotherapy. It sounds logical because even within the same cancer type and localization, individual tumors are clinically and biologically highly heterogeneous, including their radiosensitivity as well. Thus, some fractionation schedules could be highly effective for one tumor type but not for others, and the choice of total dose as a primary parameter in the tailoring of radiotherapy planning for individual patients seems in decisive enough.

Overall radiotherapy or treatment (combined) time (ORT or OTT)

Reviewing the literature in the field of the dose-time-effect relationship, it is difficult to select studies which include as many homogenous groups of cancer cases as possible regarding tumor type, localization, and stage of disease treated with radiotherapy alone, which used total doses in the narrow range, but given in a relatively wide range of the overall radiotherapy time (ORT). Such a study allows for an estimation of the TCD_{50}, i.e., the dose producing 50% of at least 3-year local tumor control (LTC_{50}), and therefore the ORT remains the only variable. Among many published papers, two studies have been found which fulfilled all the criteria mentioned earlier, and therefore were selected for the present analysis. The first one, published in 1983, concerned supraglottic cancer patients, all in the stage T3–4N0 [4, 24] and a second [17] was published in 1992 regarding cervix cancer cases in stage III where radiotherapy was the only treatment and the ORT was the only variable.

The raw data from these three studies have been used to estimate the TCD_{50} values, which was 85 ± 7 Gy for cervix cancer and 61 ± 5 Gy for supraglottic cancer. Next, only cases which received these estimated TCD_{50} doses ± 5% were selected, and at least 3-year LTC_{50} values were calculated and the LTC_{50} *vs.* ORT curves were estimated (fig. 2). For constant TCD_{50} values, the LTC values significantly depended on the ORT. For cervix cancer, an extension of the ORT from 30 to 70 days results in a significant decrease of the LTC from 90% to 35%, which gives a loss of about 1% of the LTC by one day extension of the ORT. For supraglottic cancer, the decrease of the LTC with extension of the OTT was even steeper, resulting in a reduction of the LTC by about 2.5% per each one extra day of the ORT.

These results convincingly suggest that time as a single parameter has a much higher prognostic and predictive power then the dose. However, it does not discredit (compromise) the

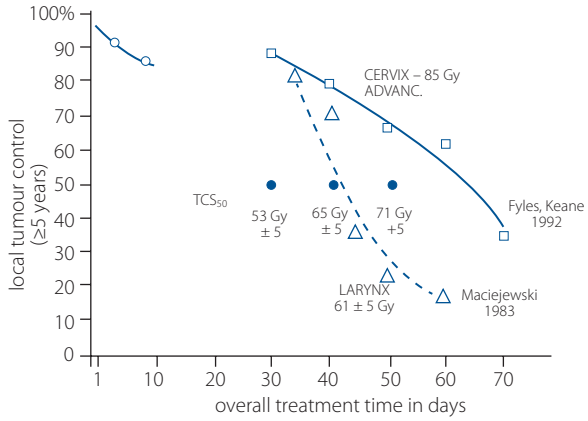

Figure 2. Local tumour control (LTC) – Dose Intensity (DI) relationship for four cancer types

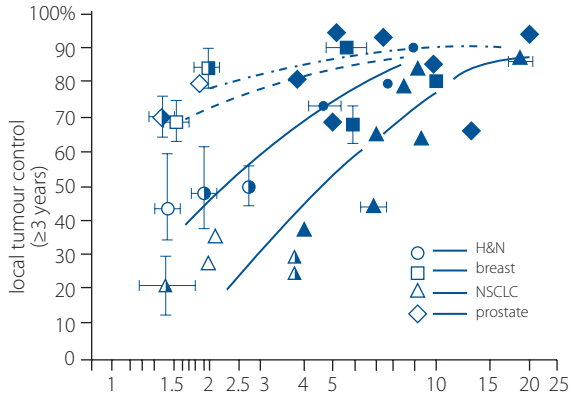

Figure 3. Local tumour control (LTC) – dose intensity (DI) relationship for four cancer types

importance of the prescribed total dose, but it does show that the ORT is more important – "the shorter the better".

A very short ORT which generally characterizes stereotactic hypofractionated radiotherapy (left top on fig. 2) strongly correlates with unexpectedly high probability of the LTC; it is not possible to separate the ORT or OTT (for combined treatment modalities) from the dose. They depend one on one another and the Dose--intensity factor (DI) quantatively expresses such a relationship. Figure 3 clearly shows that the LTC continuously improves with increasing the DI for all four analyzed tumor types and the LTC above 70% can be predicted if the DI gets higher than 5–6 Gy/day.

The paramount importance of TIME as a factor has a key and universal meaning, not only for radiotherapy as a sole treatment but also for combined therapy which is used more and more frequently. In the contrary to radiotherapy time (ORT), overall therapy time (OTT) is measured from the first to the last day of combined treatment modalities. Therefore any unnecessary breaks or delays between therapeutic modalities could significantly decrease preliminarily the predicted clinical efficacy of such a strategy.

Recently, the importance of TIME has been the major focus of the published study on intraoperative radiotherapy

(IORT) during conservative surgery for early advanced breast cancer patients in stage T1–2N0M0 with at least one risk factor, combined with postoperative chemotherapy and radiotherapy [17]. Two options of combined therapy were used. In the first, adjuvant chemotherapy was primarily used, followed by so-called delayed RT, whereas in the second, concurrent chemo-radiation was applied where OTT was about 4-times shorter (56 days *vs.* at least 235 days). As a consequence, overall DI for the first option was about 0.49 Gy/d compared with 2.25 Gy/d for the second one (tab. II). For the concurrent CHT-RT, the HR (hazard ratio) factor was 0.07, what means that this option, due to shortening the OTT, correlated with a decreased risk of local recurrence by 93% (1 – HR = 1 – 0.07 = 0.93), whereas in the first option, the HR for the delayed RT reached the highest value of 14.28. If the delayed time of the RT was longer than 20 days above an average of 60 days (HR = 1.02) than the risk of local recurrence increased by about 49% ($HR = 1.02^{20} = 1.485 \sim 49\%$). Therefore the clinical efficacy of the intraoperative IORT was in fact neglected and thereafter its use occurs unnecessary. This example clearly illustrates the leading prognostic power of the time factor. It becomes even more evident for the SHRS. In that modality the ORT is significantly shortened to 1–10 days, resulting in a tremendous increase of the DI, being in the range of 6–20 Gy/day. As a consequence, much lower total doses of 1 x 20 Gy or 3 x 18 Gy produce very high LTC (85–95%) of various tumors (fig. 2A–D, fig. 3) what not necessarily always means patient's permanent cure.

Discussion

Despite and contrary to the gathered experience over the last few decades and many well documented studies, the first decision in radiotherapy planning immutably still concentrates on the choice of total dose (TD), followed by the choice of dose per fraction, overall radiotherapy time (ORT) and the optimal 3D technique of irradiation. In the case of combined therapy, the same steps are applied and not necessarily enough attention is paid to the duration of intermodality breaks.

Thus, the ORT or OTT may differ and even be prolonged whereas the total dose does not change. The clinical consequence of such a situation is that the cell kill power of the prescribed dose significantly decreases (fig. 2 and fig. 4).

In H&N cancers, any dose escalation beyond 83 Gy, even if hyperfractionated does not significantly yield any LTC improvement [1, 3, 4, 24]. For locally advanced tumors, concurrent chemo-radiation is an optimal solution and chemo-shots during continued daily irradiation can be considered as "cell-kill boosts" resulting in LTC improvement [1–5, 24]. Even though H&N cancers are not best suited to the SHRS [20, 26], for selected early advanced small tumors, mainly localized in the midface region, it is highly effective; 24 Gy in 2 fractions or 5 fractions of 3 Gy produce about 80–85% 3-year LTC. It seems that SHRS could be feasible and a reasonable and effective option for local tumor recurrences [20, 22]. This is convincing evidence that the therapeutic power of the time factor is advantageous to the effect of the dose.

For breast cancer, the use of RT is the object of extensive discussion [7–16]. In principle, the discussion is focused on early breast cancer with or without conservative surgery. The number of the individual tumor's characteristics is continuously growing. In one recent Int J Radiat Oncol Biol Phys issue, Francis et al. [16] used as an example the case of pT1cpN0(i+) cM0, multifocal, dose margins, pleomorphic calcification, high grade Ki >50, oncotype DX24, BRCA1 and BRCA2 positive breast

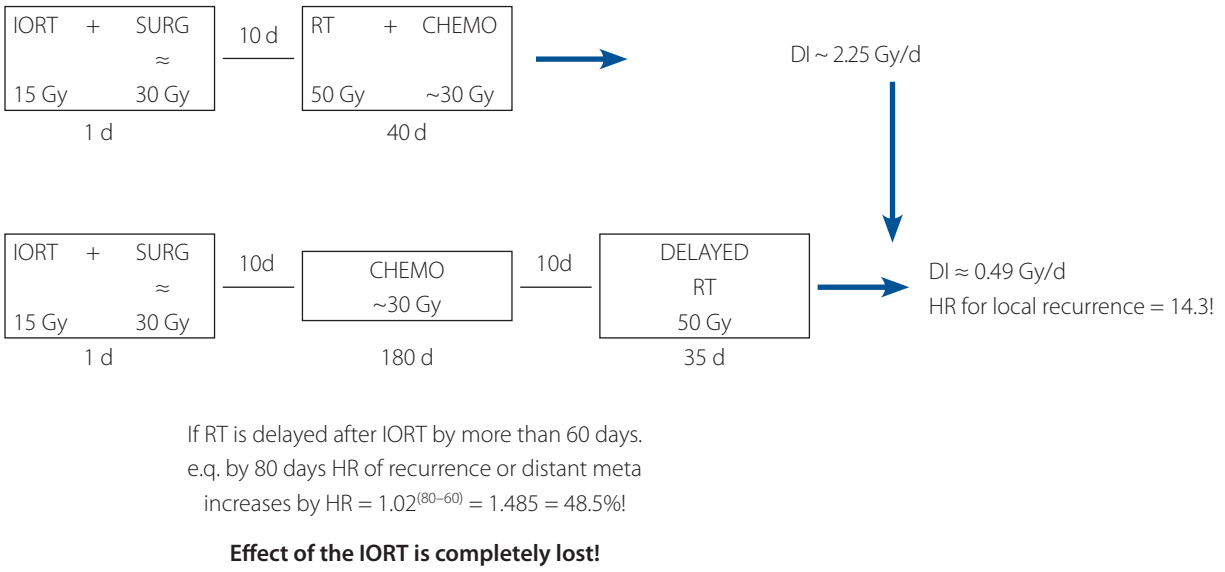

Figure 4. Two options of the IORT – conservative surgery combined adjuvant chemo- and radiotherpay for early breast cancer

cancer and the authors have raised the question to three independent experts – what would you do? Would you recommend post-op radiotherapy or not? There were no unanimous answer, with many ranging from – "yes, of course" to "not necessarily", suggesting that the risk of complications may outweigh the benefits. In 2021 Rodin et al. [7] have convincingly pointed out, based on the results of three independent trials [12–14], that standard fractionation for breast cancer is no longer standard. These trials have documented strong evidence to support stereotactic hypofractionation as optimal irradiation of early-stage breast cancers regardless of its characteristics. Various hypofractionated schedules, ranging from 26 Gy in 5 fractions to 54 Gy in 3 fractions produced high 80–95% 6–8-year local tumor control. The present review clearly supports these results (fig. 2 and 3) and simultaneously show the prognostic advantage of the time factor over the total dose.

Finally, De Paula et al. [8] and Mutter et al. [9] recommended a hypofractionated regimen of 38.5 Gy delivered in 10 fractions in the ORT of 12 days as a highly effective standard option for patients with early-stage breast cancer, which significantly shortens the ORT from about 5 weeks to only 1.5 week.

A similar conclusion concerns non-small-cell lung cancer [18–21]. Even in the 70ts Fletcher [24] pointed out that using conventional fractions of 1.8–2.0 Gy, a total dose of 100 Gy or higher might be required for local control of most NSC lung cancer, but such high doses would not be achievable without excessive toxicity. Stereotactic hypofractionated radiotherapy (SHRT) has been recognized and recommended mainly by Timmerman et al. [20] and Tateisi et al. [21] as the most favorable alternative, but it remains limited for early stage and small tumors (T1–2N0M0) and also as a postoperative treatment. Various fractionation schedules were tested ranging from 45 Gy in 3 fractions in 6 days to even 60 Gy in 3 fractions in 6 days which resulted in unexpectedly high 3–5 year LTC – from 75% to even more than 85% (fig. 1C and fig. 3). Such a high LTC corresponds with a DI higher than 7 Gy/day, which convincingly although indirectly suggests favorable and advantageous prognostic power of the time over the total dose.

Undoubtedly, prostate cancer has become a major candidate for the SHRT [22, 23, 26], and 46 Gy in 5 fractions or 40 Gy in 3 fractions in 6 days produces high, over 80% 5-year biochemical no evidence of disease (BNED). Therefore, such schedules seem to be serious challengers to conventional 78 Gy in 39 fractions in 55 days.

If combined therapy is planned instead of radiotherapy alone, the prognostic priority of time factors remain. This means that each treatment modality should be completed at the shortest OTT possible and concurrent chemo-radiation is much more effective than the sequential option due to the shortened OTT.

If each therapeutic modality, part of the combined treatment, complies with treatment time rigour, then intermodality intervals (breaks) have a kay-impact on the overall effectiveness of such a therapeutic strategy. Any delays longer than required or permissible significantly reduce overall DI, which leads to lower probability of local tumor control (LTC). A convincing example of such a risk is the use of the IORT during conservative surgery for early breast cancer combined with postoperative radiotherapy or chemoradiation [17]. If the RT was delayed after postop. chemotherapy, than a one day extension of the interval between the IORT used at the beginning of the treatment and postoperative adjuvant RT delayed above 60 days resulted in an increase of local recurrence risk by 2% per each day of the intertreatment interval. A consequence of the delayed IORT-RT interval to 80 days instead of 60 days was that the risk of local recurrence increased by 42.5%. This may strongly suggest that in fact the use of the IORT was ineffective, and likely unnecessary because the efficacy of the IORT dose was reduced almost to zero. This study strongly suggests that the OTT of the combined treatment modality becomes a paramount prognostic factor; even if each modality is planned as highly effective, any protraction of its duration over the planned limit, and any unnecessary lengthened intermodality breaks are likely to ruin the preliminary expected clinical efficacy.

Conclusions

Despite the custom of planning the dose as the first prognostic parameter, the time of radiotherapy or whole therapy plays a paramount role. Therefore the OTT (ORT) should be primarily chosen as the first parameter and the planned modality (radiotherapy) should be tailored thereafter one after another, in such a way that their duration and any intermodality breaks are as short as possible. This leads to an inverse order of the treatment parameters planning, that means the time to be the first one and followed by the dose and its fractionation.

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