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Review article

Radiotherapy

Combined CONVentional with HYPOfractionated regimen (CONV-HYPO) alternative instead of conventionally fractionated radiotherapy to improve treatment outcomes

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For years, the process of accelerated repopulation recognized as a dominant factor for radiotherapy failures has been deduced rather than proved by direct clinical data. It sounds logical and that towards the end of fractionated radiotherapy residual tumor cells likely become hypoxic and resistant to conventional dose fractions. Therefore, total doses higher than 63–65 Gy are likely wasted and useless, at least for locally advanced cancers. Thus, the last few 2.0 Gy fractions should be replaced with a few large 5–10 Gy fractions. The CONV-HYPO concept is presented and discussed in detail. For years, the CONV-HYPO has mainly been explored to treat rectal cancer, and the Papillon 50 kV unit has been most often used as a HYPO contact therapy. Recently, high dose rate (HDR) brachytherapy has become a plausible alternative due to the precise equipment entering to the market. This method is presented in detail. The CONV part of 45 Gy in 25 fractions combined with Capecitabine is followed by the three-step HYPO-HDR BRT procedure consisting of 3 × 8 Gy, 3 × 10 Gy, and if it is well tolerated, then can be followed by the last step of 3 × 12 Gy. This protocol is now used in Gliwice. However, rectal cancer is not the only target for the CONV-HYPO, as it can also be effectively used to treat H&N, lung, esophageal, liver, pancreatic, prostate cancers, and soft tissue sarcomas as well.

Keywords: hypoxic tumor cells, ineffective conventional irradiation, CONV-HYPO concept, rectal cancer, Gliwice protocol

Why conventionally fractionated radiotherapy should be abandoned?

Results of about 850 head and neck cancer patients treated by radiotherapy alone were analyzed in 1990, showing a steep increase in the total dose with extension of the overall treatment time. This tendency was interpreted as the result of accelerated population of tumor clonogens, which may counterbalance cell kill effect of even 1.4–1.6 Gy/day [1]. Repopulation potency has been considered as a dominant factor for radiotherapy failure. It is not easy to debunk such a belief that was advocated for over 30 years. However, it was indirectly deduced only, but not proven by direct clinical data. Nowadays, it looks that *"repopulation concept"* has ignored radiobiological principles and in fact it does not seem entirely reliable and true.

It has been generally accepted as a rule that the biological effects of the fraction's dose is generally counted as a constant rate of the cells killed during fractionated irradiation. However, as a matter of fact, radiation effects relate to the number

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of the tumor cells killed, which are not constant but markedly decrease towards the end of treatment. For example, if a tumor contains 1 billion cells (10^9), then after 10 conventional fractions (20 Gy) about 980 million cells will survive, which may still repopulate to neutralize a part of each consecutive fraction's dose. But after 30 fractions of 2 Gy, only 10^1–10^2 cells will survive.

It seems radiobiologically unreliable that when the number of tumor cells gets smaller and smaller after 30–35 fractions — even if they remain euoxic (but they do not) — they still will have enough potential to repopulate faster and faster than after 10–15 fractions, unless their cell cycle turnover time would is shortened by a factor of 15–20, what never happens. A plausible alternative hypothesis might be that residual tumor cells are hypoxic (continued irradiation also causes deterioration in the vascular network and oxygen supply) and dominate during the delivery of the last few dose fractions, which are too small to overcome their radioresistance to kill them all.

Hypoxic cancer cells are about 2.5–3 times more radioresistant than euoxic cells. It suggests that towards the end of irradiation, hypoxic cells likely *"ignore"* the last 5–6 fractions of 2 Gy (Fig. 1). Even if sublethal damage occurs within these cells, intracellular mechanisms can efficiently repair such damage. Therefore, the last few conventional fractions are likely ineffective; there is, in fact, no reason to escalate the total dose for locally advanced tumors to improve their clinical outcome.

Disappointing results of many altered fractionation trials (~ 6% therapeutic gain) which have been carried out for over 25 years [2] are convincing arguments for increasing importance of hypoxic tumor cells (which they dominate) during the few last fractions, the more so because fraction doses in these trials were within the narrow range of 1.15 to 2.0 Gy. It suggest that

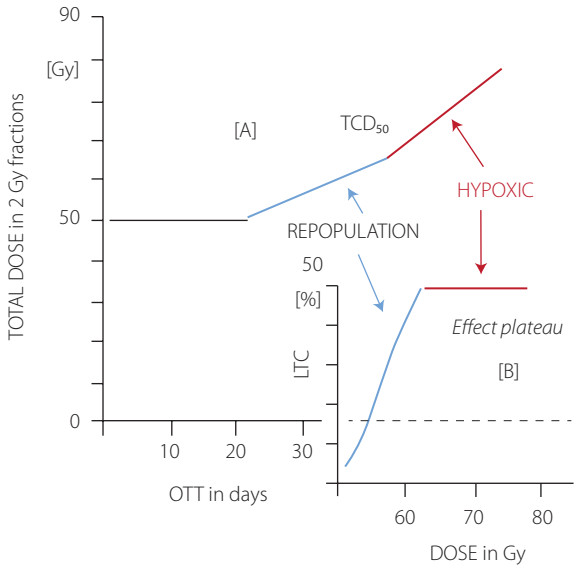

Figure 1. Dose-time relationship for head and neck (H&N) cancer corrected for repopulation and hypoxic — based on data from [1]; LTC — local tumor control; OTT — overall treatment time; TCD — total cure dose

any increase in a conventionally fractionated total dose above 63–65 Gy is likely wasted and clinically useless, at least for locally advanced cancers. Finally, if radiation oncologists expect substantial improvements in the therapeutic benefit, one should bear in mind that there is no longer room for conventional 2 Gy radiotherapy, if optimal local tumor control is expected.

CONV-HYPO dose fractionation — a promising concept

Stereotactic hypofractionated radiotherapy (SHRT) has been offered as a very promising perspective for the use of high-dose fractions in radical radiotherapy with unexpectedly high permanent local tumor control (LTC) of 85–95%, however mainly for small (< 5 cm in diameter) primary tumors [3, 4]. Sophisticated equipment (CyberKnife) and techniques, [volumetric modulated arc therapy (VMAT)] have made such therapy a plausible alternative to conventional irradiation.

It is more than likely that the residual number of tumor cells which survived previous fractions is low, about 10^2–$10^{2.5}$ cells, and they are undoubtedly hypoxic and radioresistant to conventional 2 Gy fractions. Thus, the last 5–6 conventional dose fractions delivered to locally advanced tumors are wasted (average LTC lower than 50%) since conventional dose intensity (DI) is too low (1.43 Gy/day) to overcome cell's hypoxia. The DI increases to effective 2.6–10.0 Gy/day by using the last 4–6 large fractions. Such combined radiotherapy termed as combined CONVentional with HYPOfractionated regimen (CONV-HYPO) (Fig. 2A, B) includes conventional 45–50 Gy delivered in 25 fractions, followed by 5–6 high fractions of 5–6 Gy or 3 fractions of 10 Gy. The CONV part can be intensified by concurrent chemotherapy to enhance cell kill effects (Fig. 2B). External 5–6 stereotactic hypofractions can easily be given using brachytherapy. Figure 3A shows that 2 Gy fractions of conventional radiotherapy (RT) alone result in successive tumor deceleration, partly neutralized by clonogenic cell repopulation after week 2–3 of treatment. However, when finally 10^1–10^2 cells will survive they are hypoxic, and radioresistant, and they do not respond to 2 Gy fractions (horizontal *"effect plateau"* on Fig. 3A), since the overall biologically effective dose (BED) is low, not higher than ~ 73 izoGy.

Among various altered fractionation schedules tested in clinical trials, Kian Ang [5] proposed a so-called *"concomitant boost"* using conventional fractions given once-a-day during the first few weeks followed by twice-a-day doses of 1.8 Gy and 1.5 Gy during the last two and half weeks. The results showed far from impressive improvements of the LTC, since all fraction doses were below 2 Gy.

The CONV-HYPO alternative consists of two parts (Fig. 2). The first one is just conventional fractionation of 45–50 Gy in 25 fractions, which have the task to eradicate microscopic spread of cancer cells beyond the gross tumor mass, and to produce a partial regression of the primary tumor. The HYPO part is realized by using a few large fractions of external irradiation

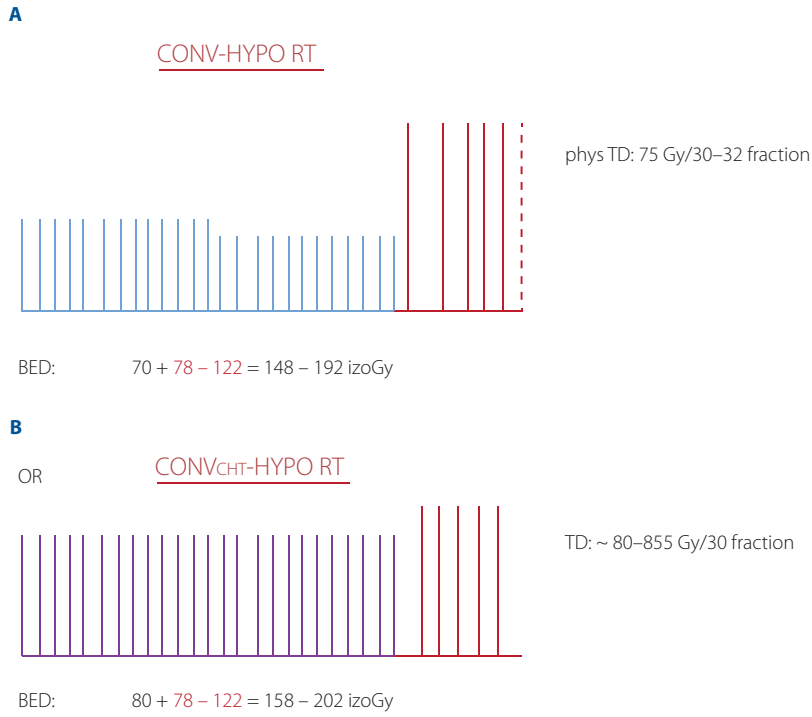

Figure 2. Combined CONVentional with HYPOfractionated regimen (CONV-HYPO) fractionation pattern; **A**. Radiotherapy alone, lower dose fractions after 25 Gy theoretically illustrates lowered dose fractions due to neutralizing effect of repopulation; **B.** Combined chemoradiation of the past (CONV). Total biologically effective dose (BED) doses are calculated using α/β value of 6 Gy; CHT — chemotherapy; RT — radiotherapy; TD — total physical dose

or of brachytherapy with hypofractionations of 3 × 10 Gy or 5 × 6–7 Gy, focused on the residual tumor GTV, to eliminate the surviving, mainly hypoxic cells. Although the DI of the first part is low (1.43 Gy/day), the DI of the second part is very high (8–10 Gy/day) which can effectively eliminate residual resistant hypoxic cells. Such a combination of the two different parts of irradiation vary in their biological potential, even if its physical total doses do not differ very much. Although the degree of biological power of the DI during of the first part is about 7-times lower than the second, it is still effective enough to sterilize euoxic tumor clonogens, mainly those localized beyond the gross tumor mass, but it is ineffective in eradicating residual hypoxic cells, which become the target for the HYPO part.

The biological effect is not linearly related to the radiation dose [6–8], and its relationship becomes increasingly supra--linear as the dose increases. Thus, in terms of the cell kill, doses of 3 × 10 Gy are much more effective than the same total dose delivered in 15 fractions of 2 Gy. Due to highly conformal radiotherapy, the total dose that may be given to the tumor is not in fact entirely and always limited by the tolerance of the adjacent normal tissues [8] since the residual tumor volume is very small. Nevertheless, the HYPO total cure dose (TCD) should be weighted as optimal for tumor control, and in the same level, as maximal tolerance doses (TTD_{max}).

The Linear-Quadratic formula (L-Q) has been used to count biologically effective doses [8], since an α/β ratio represents the sensitivity of the tumor or critical normal tissues to change in dose per fraction (it has nothing to do with its intrinsic radiosensitivity).

Dale [6] used an α/β formula to count the effective biologically equivalent dose if given in 2 Gy fractions ($EQD_{2.0}$). The $EQD_{2.0}$ quite well represents fraction doses lower than 5 Gy but not large HYPO fractions, since it underestimates the real value of the biological dose. Fowler, Joiner and van der Kogel [7, 8] have suggested to use the following biological effective (BED) dose formula which gives reliable estimates:

$$BED = TD\ (1 + di / \alpha/\beta),$$

where TD is the total physical dose, and di — the dose per fraction. For tumors, an α/β value is in the range of 10–25 Gy (usually 10 Gy) suggests that the tumor cells for the size of the dose per fraction is not very important, whereas for normal tissues since the α/β ratio is usually in the range of 2–5 Gy (highly sensitive to change in the dose per fraction). Therefore it is essential to count the BED value of the HYPO part for critical normal tissues surrounding the tumor because the BED for the CONV part does not change a lot (Tab. I). Moreover, D_{10} (dose reducing the cell number by 1 log, i.e. 10^9 to 10^8, or 10^3 to 10^2) for the HYPO and the CONV differ significantly (about 3.5 Gy *vs.* 7 Gy). For example, 36 Gy in 4–6 fractions will reduce cell survival from 10^9 cells to 10^{-1} since $10 \times D_{10}$ (36 Gy : 3.5 Gy) decelerates the cell number by 10 logs whereas the same total

dose given in 2.0 Gy fractions (36 Gy : 7 Gy = 5 × D_{10}) will reduce the cell number by only 5 logs, e.g. from 10^9 to 10^4, and therefore it will not produce any LTC. It argues against normalization of the HYPO total dose to be biologically equivalent if is given in 2.0 Gy fractionations and therefore advantage of the BED formula is much more reliable.

Theoretical cell survival curves (Fig. 3) show that when cancer cell deceleration after conventional dose fractionation reaches a level of about 10^3–10^2 cells (Fig. 3A) one cannot expect the LTC higher than 50% if the irradiation continues, since the residual cancer cells are likely hypoxic and therefore they do not respond to the successive 2 Gy fractions. The first CONV part with 45–50 Gy in 25 fractions (Fig. 3B) can easily eradicate the microspread of cancer cells [for example 7 × D_{10} (7 × 7 Gy) will reduce cell number from e.g. 10^6 (microcellular lesion) to 10^{-1} cell, what would result in about 90% LTC of such micro lesions]. Moreover, the HYPO part with a few large fractions (SHRT or BRACHY can effectively eliminate residual hypoxic cancer cells (Fig. 3B) and furthermore, in some cases it may also offer some organ preservation — important for the patient's continued quality of life.

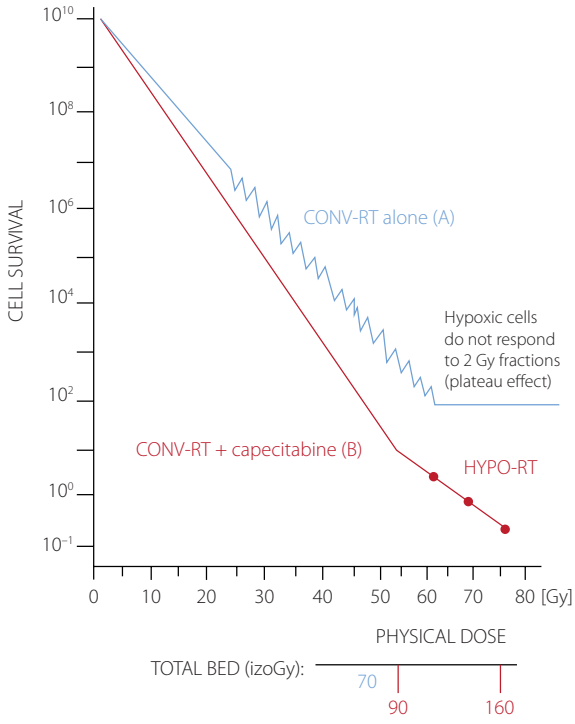

Figure 3. Tumor cell survival curve for (**A**) classical conventional radiotherapy (RT) alone (blue line), (**B**) combined CONVentional with HYPOfractionated regimen (CONV-HYPO) schedule (red line). Horizontal part of the curve A means no response to the escalated doses above 60–65 Gy (due to domination of hypoxic cells); BED — biologically effective dose

CONV-HYPO for rectal cancer

The CONV-HYPO is an approach of the dose fractionation which is an effective alternative to conventional radiotherapy for various tumor types and localization. For head and neck, lung, liver, prostate, kidney, bladder cancers, and various sarcomas the SHRT can also be used as a HYPO module. For bronchial esophageal, and rectal cancers, the HYPO-brachytherapy offers an optimal dose distribution in the tumor volume (GTV) and more effective protection of the epithelium of the tube-like organs and the preservation of their function. For the last 50 years the rectal cancer has been the most often object of the CONV-HYPO to preserve the rectal sphincter. In 1975, Papillon, as a pioneer introduced the contact 50 kV X-ray radiotherapy for early pollypoid rectal cancer [9]. At 5 years the surgery-free survival with good bowel function was about 83%. The Lyon R 96–02 phase III trial showed that X-ray contact therapy combined with external radiotherapy improves sphincter preservation in patients with cT_2–T_3 cancer of the distal-middle rectum and it resulted in a high 10-year local tumor control (Fig. 4). Renaissance of contact X-ray therapy has begun around 2009 when a new 50 kV machine called Papillon 50^{TM} was manufactured, and around 2018, 11 Papillon systems were installed mainly in the UK and in France [10]. Over 1000 rectal cancer patients have been already treated with contact X-ray therapy combined with chemoradiotherapy. Gérard is one of a few European radiation oncologists with enormous experience in the use Papillon 50^{TM} therapy for T_2–T_3N_{0-1} rectal cancer [11–17]. Recently, the GEC ESTRO ACROP has issued consensus recommendations for contact brachytherapy for rectal cancer [18].

Papillon 50 kV approach is a contact radiotherapy and the dose is planned on the surface of the tumor, which results in gradual deceleration of the superficial tumor cells, layer by layer (X-rays beam has the RBE value of 1.4–1.8 compared to 1.0 for high energy photons). Based on to the inverse square law, the penetration (percentage of depth dose) is higher using contact X-ray than for high dose-rate brachytherapy.

Table I. Biologically effective doses (BED) estimated for the combined CONVentional with HYPOfractionated regimen (CONV-HYPO) for rectal cancer as tolerance doses (using α/β value = 6 Gy)

STEP	CONV Fx schedule	BED CONV Fx	HYPO Fx schedule	BED HYPO Fx	HYPO Fx BED relative to 15 × 2 Gy (1.0)	TOTAL BED
I	45–50 Gy/25 fx	61.2–70 izoGy	3 × 8 Gy	78 izoGy	1.9	139.2–148 izoGy
II	–II–	–II–	3 × 10 Gy	90 izoGy	2.1	151–160 izoGy
III	–II–	–II–	3 × 12 Gy	122.4 izoGy	2.9	183.6–192 izoGy

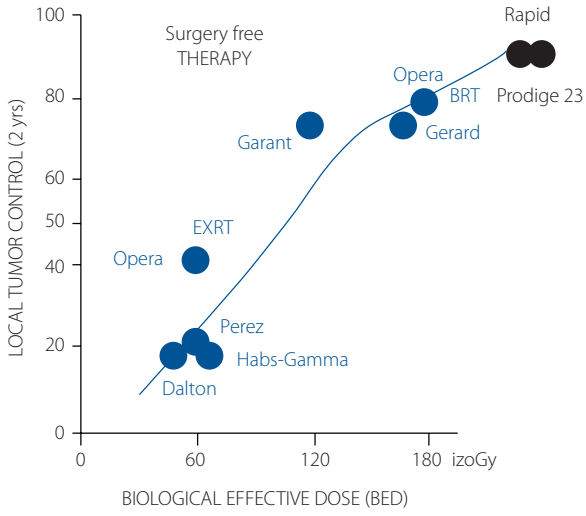

Figure 4. LTC-DOSE escalation relationship for the combined conventional with HYPO fractionated regimen (CONV-HYPO ± chemotherapy) for surgery – free rectal cancer (adapted from Gerard et al. [15]), the EQD doses calculated by Appelt [19] are converted into biologically effective dose (BED) using α/β value of 6 Gy; BRT — brachytherapy; EXRT — external irradiation

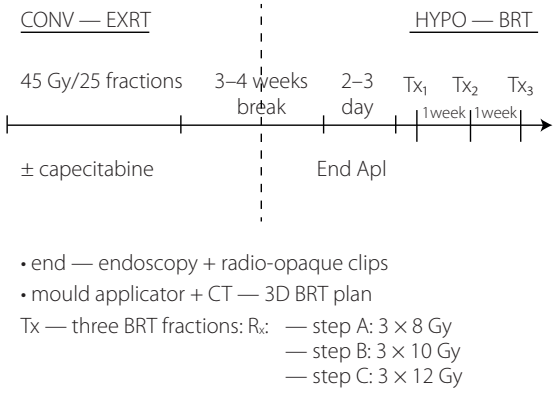

Figure 5. Work flow of CONVentional with HYPOfractionated regimen brachytherapy [CONV-HYPO (BRT)] — Gliwice protocol for surgery-free therapy of rectal cancer patients; CT — computed tomography; EXRT — external irradiation

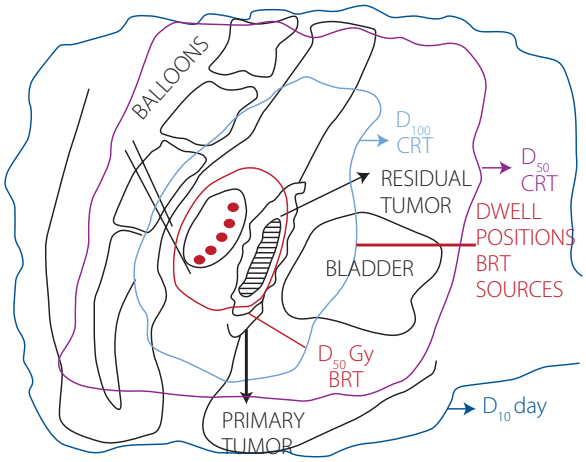

Figure 6. Example of dose distribution of the CONVentional (CONV) combined with high-dose HYPOfractionated brachytherapy (HYPO BRT) planned by Kraszkiewicz and Wojcieszek for local rectal cancer. The step 2–10 Gy is planned for BRT; CRT — conventional RT

The Papillon 50 kV therapy is limited to T_1, T_{2-3} N_0 tumors (≤ 4 cm in diameter) localized in the distal and middle part of the rectum, which must be accessible to the rectal application of the X-ray tube. Contact X-ray therapy has sometimes been given first, followed by chemoradiation (with Capecitabine) and provided the 3–5 year local tumor control (Fig. 4) and overall survival close to 85% [15, 17].

Alternative to the Papillon 50 kV is a high-dose rate endorectal brachytherapy (HDR BRT) with the use of high quality imaging for tumor visualization, and the 3D-treatment conformal planning [19–21]. Since 2005, due to the development of the intracavitary mould applicator (Nucletron), the HYPO-HDR BRT (high dose brachytherapy) has become a useful alternative to contact 50 kV therapy. By contrast with HYPO — 50 kV technique with the planned dose on the tumor surface, decreasing along with the tumor depth, in the HDR BRT the planned dose is estimated for the bottom-baseline of the tumor which increases towards its surface. Treatment planning and dose delivery is realized using the intracavitary mould applicator and a microselection remote after-loading device (Nucletron) using to real-time implementation of the 192Ir (Iridium-192) sources.

The first part of the HYPO-BRT starts 3–4 weeks after completing the delivery of 45–50 Gy of the CONV external irradiation, and consists of the radio-opaque clips inserted to the tumor during endoscopy to marks and visualize tumor position (Fig. 5). After 2–3 days, mould applicator with two balloons are inserted to the rectum under-mild intravenous anesthesia. When the device is in the desired position, the balloons are inflated with water to immobilize the applicator. The ipsilateral balloon flattens the tumor to receive the planned dose distribution within the defined GTV, whereas the contralateral one displaces normal rectal mucosa opposite to the tumor [20]. According to the old Manchester-McComb and Quimby law, the ipsilateral balloon also improves homogenous dose distribution within the tumor GTV.

Once the applicator is immobilized, serial computed tomography (CT)-based HDR BRT treatment planning is carried out using 3D dose calculation (PLATO system) for the tumor GTV based on serial CT images. For treatment planning, only dwell positions in catheters proximal to the tumor are selected. The PLATO *"real time"* planning system also provides an option to plan optimal dose distribution, highly conformal to the target volume, with a proper sparing of the surrounding critical normal structures. When a satisfactory plan is confirmed (Fig. 6 and 7), the central tungsten shield is placed before the start of the treatment. This original technique designed by Te Vuong [20] is adapted by Kraszkiewicz and Wojcieszek to realize

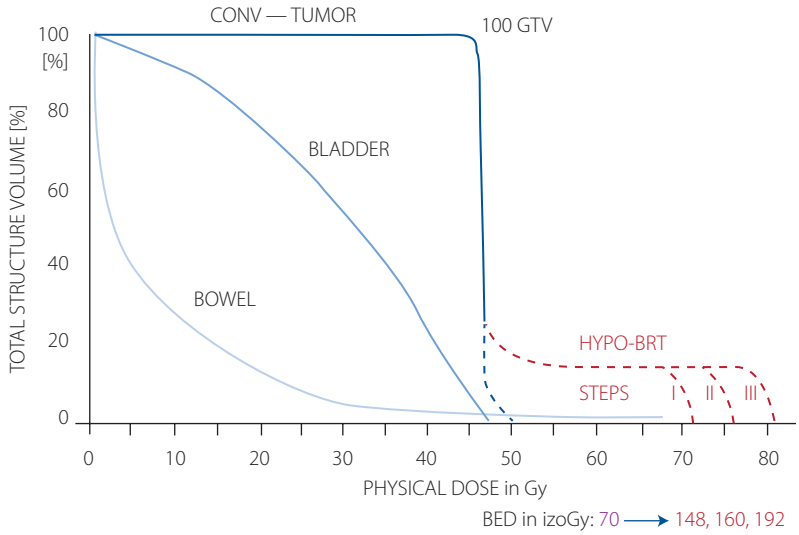

Figure 7. Cumulative dose volume histogram for combined CONVentional with HYPOfractionated regimen (CONV-HYPO) planning example shown on Figure 5; BED — biologically effective dose; BRT — brachytherapy

in Gliwice the three-step- treatment-protocol for T_2–T_3 N_0 rectal cancer. To optimize the size of high dose fraction, in the first step 3 fractions of 8 Gy are planned. If such schedule will be well tolerated, then the patients will be recruited to the second step using 3 × 10 Gy, and finally if it will also be well tolerated then the third step with 3 × 12 Gy is planned. The respective BED doses are shown in Table I. Since the tumor regression progressed slowly, diagnostic biopsy can be performed not sooner than six months after completing treatment.

The CONV-HYPO therapy used to treat rectal cancer is just an example of an wide spectrum of the use this approach including other tumor types and localization as lung, esophageal, head and neck cancers and soft tissue sarcomas, with or without concurrent chemotherapy, as a sole or postoperative therapy to improve long term local control and disease free survival. Therefore, there is no longer radiobiological and clinical arguments to continue and escalate conventionally fractionated radiotherapy, since for years it has not resulted in a pronounced improvement of the long-term efficacy so far. It seems reliable that this traditional fractionation should no longer be continued, even for palliative radiotherapy.

Article information and declarations

Authors contributions

Bogusław Maciejewski — conceptualization, methodology, writing – original draft preparation, writing — review & editing.
Małgorzata Kraszkiewicz — conceptualization, writing — original draft preparation.
Piotr Wojcierszek — data correction, methodology, writing — original draft preparation.
Jean-Pierre Gerard — conceptualization, validation, writing — review & editing.

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Conflict of interest

None.

Supplementary material

None.

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