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To boost or not to boost in radiotherapy

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Aim. The aim of this paper it to analyse and discuss standard definition of the "boost" procedure in relation to clinical results and new forms of the boost designed on physical and radiobiological bases.
Material and methods. Seventeen sets of clinical data including over 5000 cases cancer with different tumour stages and locations and treated with various forms of "boost" method have been subtracted from literature. Effectiveness of boost is analyzed regarding its place in combined treatment, timing and subvolume involved. Radiobiological parameter of D10 and normalization method for biologically equivalent doses and dose intensity are used to simulated cold and not subvolumes (hils and dales) and its influence of effectiveness on the boost delivery.
Results. Sequential and concomitant boost using external irradiation, although commonly used, offers LTC benefit lower than expected. Brachytherapy, intraoperative irradiation and concurrent chemotherapy boost methods appear more effective. Conformal radiotherapy, with or without dose-intensity modulation, allows heterogeneous increase in dose intensity within the target volume and can be used to integrate the "boost dose" into baseline treatment (Simultaneous Integrated Boost – SIB). Analysis of interrelationships between boost-dose; boost volume and its timing shows that a TCP benefit from boosting can be expected when a relatively large part of the target volume is involved. Increase in boost dose above 1.2–1.3 of baseline dose using "standard" methods does not substantially further increase the achieved TCP benefit unless hypoxic cells are a problem. Any small uncertainties in treatment planning can ruin all potential beneficial effect of the boost. For example, a 50% dose deficit in a very small (e.g. 1%) volume of target can decrease TCP to zero. Therefore boost benefits should be carefully weighed against any risk of cold spots in the target volume.
Conclusions. Pros and cons in discussion of the role of boost in radiotherapy lead to the important practical conclusion that specifying "100% of prescribed dose to 95% of the target volume is not safe enough because it permits as much as 5% of the tumour volume to be underdosed to a possibly dangerous degree. Other constraints are needed, such as minimum target dose or requiring the tumour EUD (Equivalent Uniform Dose) to be not smaller than the prescribed tumour dose. In order to achieve the expected effect of "burn-down" boost (optimal TCP benefit) the boost dose should be tailored to the number of decades of surviving tumour clonogens needing to be killed by the boost.

Czy należy stosować „*boost*" w radioterapii?

Cel. Celem opracowania jest ocena i dyskusja odnośnie standardowej definicji „dawki uzupełniającej (boost)" z wykorzystaniem opublikowanych danych klinicznych oraz nowych sposobów stosowania tej metody.
Materiał i metody. Analiza dotyczy 17 badań klinicznych, obejmujących ponad 5000 przypadków raka o różnej lokalizacji i zaawansowaniu, w których zastosowano różne formy metody „boost". Jej skuteczność oceniano w odniesieniu do miejsca „boostu" w sekwencji leczenia skojarzonego, czasu trwania i objętości tkanek napromienianych „dawką uzupełniającą". Parametr radiobiologiczny D10 oraz metoda normalizacji dawek biologicznie równoważnych i intensywności dawki użytej w celu symulacji „zimnych i gorących" ognisk w rozkładzie dawki promieniowania oraz ocena ich wpływu na skuteczność dawki uzupełniającej.

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Wyniki. Najczęściej stosowana metoda współistniejącego boostu (concomitant boost) z użyciem zewnętrznej wiązki promieniowania, przynosi zysk terapeutyczny, ale niższy od oczekiwanego (13%). Inne formy „boost" z użyciem brachyterapii, radioterapii śródoperacyjnej i chemioradioterapii są bardziej skuteczne. Terapia konformalna bez lub z użyciem modulacji intensywności dawki umożliwia niejednorodny wzrost intensywności dawki promieniowania w obszarze tarczowym. W konsekwencji dochodzi do integracji dawki „boost" z podstawowym napromienianiem (Równoczesny Zintegrowany Boost – SIB). Analiza zależności między wartością dawki „boost", czasem jej podania i napromieniania oraz objętością wykazała, że można oczekiwać zysku terapeutycznego, jeżeli obszar „boost" jest względnie duży. Wzrost dawki „boost" powyżej 1.2-1.3 dawki podstawowej zasadniczo nie zwiększa uzyskanego zysku terapeutycznego. Jakakolwiek, nawet mała niedokładność w planowaniu leczenia, prowadząca do obniżenia dawki promieniowania o 50% w 1% objętości tarczowej, niweczy każdy, nawet najwyższy zysk terapeutyczny wynikający z zastosowania „boost", a nawet więcej, powoduje obniżenie TCP do zera. Dlatego zysk terapeutyczny, wynikający z zastosowania metody „boost", należy odnosić do ewentualnego ryzyka „zimnych ognisk" w objętości tarczowej.
Wnioski. Ocena miejsca i znaczenia „dawki uzupełniającej (boost)" w radioterapii wskazuje, że specyfikacja 100% dawki, przepisanej w 95% objętości tarczowej, nie jest dostatecznie bezpieczna, ponieważ pozostałe 5% objętości tarczowej jest niedodawkowane, o różnym stopniu niebezpieczeństwa. Konieczne jest przyjęcie dodatkowych kryteriów, takich jak minimalna dopuszczalna dawka w obszarze tarczowym lub wymóg wartości dawki EUD (Dawka Jednorodnie Równoważna), nie niższej niż dawki przypisana. Ponadto, aby uzyskać spodziewany i optymalny zysk terapeutyczny (burn-down) po zastosowaniu metody „boost", dawka dla tej metody powinna być szacowana w relacji do liczby rzędów komórek klonogennych, które należy wyjałowić.

Key words: radiotherapy, boost dose, dose-time-volume non-linearity
Słowa kluczowe: radioterapia, dawka uzupełniająca, nieliniowa zależność dawki-czasu-objętości

Introduction

To find a source of the term "boost" one should move back to Baclesse, who introduced, in the nineteen thirties, the shrinking field technique based on the belief that the core of a tumour is more radioresistant than its periphery. Demonstration in the fifties of the existence of a hypoxic component in the tumour brought another rationale for that technique. Three decades later, there was still a strong belief that overall treatment time may not be critical above 6 weeks and long treatment times could be used for large infiltrative tumours. However, the high doses necessary to control gross masses can not be given to large volumes and therefore extra doses need to be delivered with interstitial therapy or with a shrinking field technique. These principles became central to the planning of the majority of external irradiation treatments. In 1966, in the first edition of the *"Textbook of radiotherapy"* Gilbert H. Fletcher defined so-called *"cone-down boost"* writing *"…the dose given through small portals over residual disease is called boost, but it is not a boost in the biologic sense since it is given to obtain the same probability of control as for subclinical aggregates"* [1]. Since that time the term "boost" has been unalterably used to describe an escalation of dose which may define either a real "biological" boost or a "false" boost in an increasing number of clinical situations.

Nowadays, it seems interesting to discuss whether Fletcher's original definition has outlived all technological and fractionation innovations or should it be revised. The important questions regarding boost terms include whether they are useful and when and how they should be given.

"Boost" variations

Since the nineteen sixties, for several decades the boost has been simply interpreted as an additional dose (sometimes termed dose escalation) restricted to the reduced target volume being at the highest risk of local failure. Therefore, the boost schedule has been intuitively and inseparably linked to the shrinking field technique. One of the most popular methods until the 1990s was to deliver the boost dose to shrunken field(s) directly after completing the baseline dose given to a large field (Figure 1A). Increase in total dose was usually accompanied by extension of overall treatment time. When the kinetics and importance of accelerated repopulation was documented and quantified such a boost regimen has been recognized to be of lower effectiveness although it may still be useful for slowly proliferating tumours.

Concomitant boost therapy (CBT) was introduced in MD Anderson Cancer Center in Houston [2] as a "boost" dose delivered to the reduced volume during the time of irradiation of a large field rather than afterwards. Usually the CBT is given as a second daily fraction (with 6h interfraction interval) in the necessary number of days in the last 2-3 weeks of treatment. In principle it could also be delivered in the first 2-3 weeks or during the whole course of treatment (Figures 1, B1 and B2), but these sequences were shown to be less effective. The use of this concomitant form of boost has been accompanied by the "field within the field" technique in the daily practice in radiohterapy.

Some modifications of the CBT include the use of an extra daily fraction on Saturday (Figure 1E) or on Saturday and Sunday (Figure 1F) throughout the whole course of radiation treatment, delivered to a smaller field

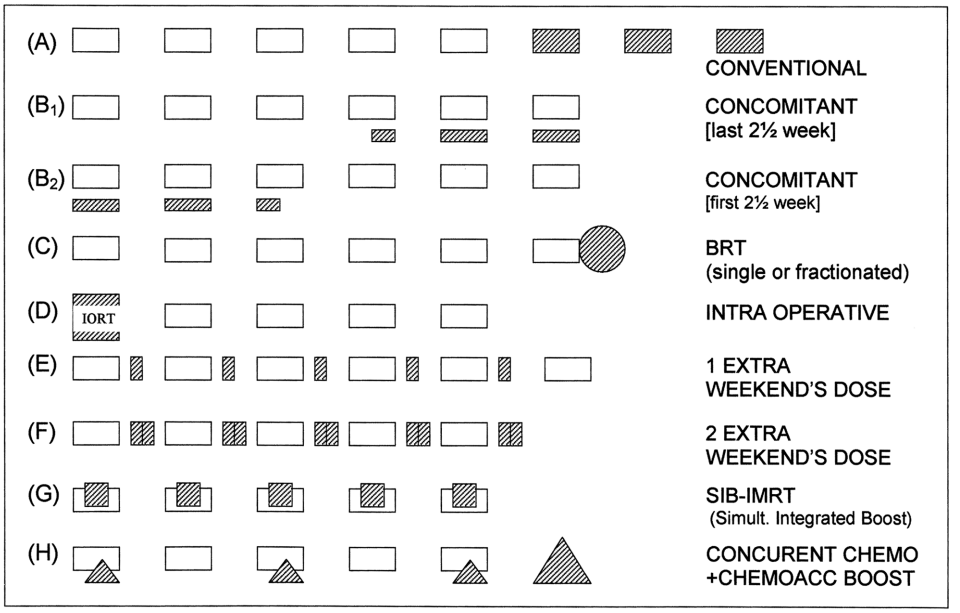

Figure 1. Graphical schemes of different "boost" regimens

within the large field [3, 4]. These modifications allow completing the treatment without extending overall treatment time (OTT) and may even shorten it by one week or more.

Brachytherapy boost (Figure 1C) has been known since Fletcher's era, but it became more widely used when the technology of High-Dose and Pulse-Dose afterloading equipment and sonography guidance were developed. An advantage of this form of boost is the possibility of delivering a high dose as a single-shot or in a few fractions to a precisely defined target and with large dose gradients beyond the reference treatment region.

New imaging techniques, (EPID, sonography) allow frequent control of the beam set-up and real-time corrections. Three dimensional conformal stereotactic radiotherapy, or single dose radiosurgery also has a possible role for additional dose escalation as a less invasive boost technique than conventional brachytherapy boosts [5, 6].

As a result of the pioneering work by Abe et al [7] at the University of Kyoto, there has been an increasing interest in the clinical application of intraoperative radiation therapy (IORT) as a single dose boost delivered directly to the tumour bed (Figure 1D). A large variety of applicators of different sizes and geometry allow tailoring of irradiation to the individual anatomy and topography of the tumour bed. A biological rationale for IORT is to escalate the dose in an area of highest tumour cell concentration. Although IORT precedes postoperative radiotherapy by a few weeks it has been found highly effective for rectal cancer with complete resection, esophageal, and pancreatic cancer and as a boost during breast conserving therapy [8, 9]. Compared to other boost methods, the advantage of IORT is direct visualization of the tumour bed during surgery, which enhances accurate dose delivery.

The new technology of dose intensity modulation (IMRT) has brought the promising opportunities to deliver both fractions, basic and boosting, during the same treatment session. The IMRT plan is designed to treat simultaneously with the "sliding window" the primary (GTV) and secondary targets at two different fraction sizes. This method (Figure 1G) is called Simultaneous Integrated (infield) Boost (SIB). Each of the specified targets receives different doses per fraction and total doses whereas number of fractions and overall treatment time (OTT) is the same for all the targets [10, 11].

Chemotherapy has always been recognized as a modality different from radiotherapy, although combinations of both (neoadjuvant or adjuvant) have been commonly used. Until recently the therapeutic gain was found to be much lower than expected. Chemotherapy was considered, theoretically, as a chemoaccelerated boost-bolus given after completing a baseline course of radiotherapy. From a biological point of view however, a single dose of drug, no matter how large it could be, will kill only a certain fraction of tumour cells surviving after the baseline course. Therefore it is more reasonable to administer cytostatic agent(s) in a few (fractionated) sessions during radiotherapy. This concept led to concurrent chemoradiation (CHTc) which can be considered as another form of boost (Figure 1H). The main objective in the CHTc is to explore drug–radiation interactions to maximize tumour radioresponsiveness. Chemo-boost administration, e.g. one a week or daily, depends primarily on the mechanisms of radioenhancement of the tumour response and toxicity to normal tissues. Therapeutic benefit occurs only when the enhancement of tumour response is greater than the toxic effect. Recently, a few studies have been designed which test a combination of two different forms of the boost i.e. IORT+CHTc, or CBR+CHTc [9].

Evidence of boost benefits

Material and methods

We took seventeen data sets including, altogether, more than 5000 patients with different tumour types, stages and localizations from the literature to review various "boost' regimens and to evaluate their efficacy. Large clinical trials, well-known studies and some pilot and phase I studies have been chosen to present a wide spectrum of "boosting". Boost-efficacy was evaluated using local tumour control gain as an end-point, meaning, an increase in at least 3-year local tumour control compared with a conventional control arm or a historical group. Acute and long-term normal tissue toxicity was not evaluated presently.

Results

The first evidence of a pronounced, although negative effect of fractionated boost dose involving extension of overall treatment time came from the RTOG 83-13 trial (Table Ia), where the boost dose of 9.6 Gy delivered in twice-a-day fractionation during an extra 5-6 days was added to the baseline total dose of 72 Gy in 42 days for head and neck cancer [12]. Almost no gain in local tumour control (LTC) was noted compared with the basic treatment. This result supports Fletcher's intuition that such a form of boost is in fact a "false" boost in the biological sense, and this is not a way in which the boost should be given, because the repopulation in the extra overall time cancels out any extra cell kill from the higher dose.

A new concept of concomitant boost (CBT) was presented by Knee in 1986 as described by Ang et al [2] and RTOG 9003 trial [13]. In the first study a boost of 18 Gy in 1.5 Gy fractions was delivered as a second daily fraction for the first or the last two and half weeks of treatment or twice-a-week during the whole course of the basic six-week irradiation using 1.8 Gy per fraction to the larger field. The authors observed that the CBT given at the last part of therapy produced a 13% higher gain in LTC than the other two forms of the CBT (Table Ib,c). However, when this beneficial form of CBT was tested in a four-arm trial RTOG 9003 the LTC was only 8% over the conventional 70 Gy in 49 days.

Yan and associates [13] used a fractionated boost dose of 20-35 Gy to residual nasopharyngeal tumours after the basic 70 Gy in 49 days (Table Ic) and they observed a 23% reduction in local recurrence compared with the group in which treatment was stopped after 70 Gy. However, the price to pay was a 3-fold increase in the incidence of radiation myelopathy (from 5.5% to 17.5%).

Yavuz et al [14] and Pos et al [15] administered two different forms of CBT to locally advanced bladder cancer (Table Id,e). In the former study 45 Gy in 1,8 Gy daily fractions was delivered to the whole pelvis (PTV_1) within 5 weeks (OTT). In addition, all patients received a CBT of 22.5 Gy (15 x 1.5 Gy) to the tumour volume (PTV_2) during the third to fifth week of treatment as a second fraction per day, to a total dose of 67.5 Gy. The authors noted a 19% increase in the LTC compared with a historical group and very low incidence (1%) of severe late complications. In the second Amsterdam study the authors went even further, by shortening the overall treatment time to 28 days. Small pelvic fields were irradiated to a baseline dose of 40 Gy in 2 Gy daily fractions (PTV). A daily CBT fraction of 0.75 Gy was delivered to the tumour area (GTV) immediately after irradiation of the large fields, resulting in a total tumour dose of 55 Gy in 2.75 Gy fractions. The LTC gain was almost two times lower (10%) compared with the Yavuz study, and severe late toxicity was surprisingly higher (13%). Even after allowing for the difference in dose per fraction it is difficult to explain the difference in the LTC and late toxicity between these two studies.

One extra daily fraction per week given in consecutive weekends with shortened OTT by one week and using a field within the field technique can be considered as another form of accelerated concomitant boost (Table I m,n). The DAHANCA 7 trial used 5 boost doses of 2 Gy on five Saturdays with OTT shortened by 1 week and achieved a 10% gain in the LTC [3]. In the CAIR [4] trial the boost of 9 or 10 fractions of 2.0 Gy or 1.8 Gy delivered in consecutive Saturdays and Sundays and with a shortened OTT of 40 days produced a LTC gain of 43% (72% vs. 31%). The basic total dose delivered to the large fields was almost the same in both trials. However, the results of CAIR should be interpreted carefully, since this trial included a relatively small number of 100 cases because it was closed early for ethical reasons (unexpectedly high gain in the LTC).

For the last 5 years Dose-Intensity Modulated Radiotherapy (IMRT) has brought a new interesting option for the boost. Using inverse planning and IMRT, a treatment plan can be generated to deliver radiation doses to two or more distinct volumes, therefore primary and secondary targets are treated simultaneously using different fraction sizes and different total doses, but given with the number of fractions and OTT remaining constant. Such a form of boost is defined as Simultaneous Integrated (infield) Boost-SIB (Table I o,p). This form has been found feasible [10, 11, 16] but still should be considered experimental because follow-up is too short to evaluate its efficacy and toxicity [17, 18]. Because of too little data in partial normal tissue tolerances within volumes irradiated with sharp dose gradients, biological models such as NTCP, BED, EUD are not applicable in the context of SIB. However, SIB has potential benefits of increased tumour cell kill and increased probability of local tumour control based on the small volume of the boost. In addition SIB shortens planning time and the overall treatment time.

Another form of IMRT-boost with dynamic MLC has been introduced in the Sloan Kettering Cancer Center in New York and in Chang Gung Hospital in

Table I. Different schedules of boost-dose with its efficacy measured as therapeutic gain in local tumour control (≥ 4 yrs.)

No.	TUMOUR SITE/STUDY	BASIC TOTAL DOSE in Gy/Time in days (T)	BOOST FORM (see Fig.1)	BOOST DOSE in Gy (% of total dose)	EXTRA BOOSTING TIME in days	OVERALL TOTAL DOSE in Gy/OTT in days IN DAYS	THERAPEUTIC GAIN in (≥3 yrs.)	Author
a.	Head & Neck, RTOG 83-13	72 Gy*/42 d	**(A)** – ERT	**9.6 Gy*** (12%)	5 – 6 d	81.6 Gy /48 d	**1%** (n.s.)	Cox [12]
b.	Head & Neck, MDACC, Houston RTOG 9003	54 Gy/42 d	**(B_1 vs. B_2)** – ERT **(B_1 vs. conv)** – ERT	**18.0 Gy** (25%) **18.0 Gy** (25%)	Last 2 1/2 wks within T	72.0 Gy/ 42 d 72.0 Gy/ 42 d	**13%** (71% vs. 66%) **8%** (54% vs. 46%)	Ang [2] Fu [13]
c.	Nasopharynx, China	70 Gy/49 d	**(A)** – ERT	**20-25 Gy** (22%)	14 – 16 d	90.0 Gy/65 d	**23%** recurr. reduction	Yan [14]
d.	Bladder ASC BRT	45 Gy/35 d	**(B_1)** – ERT	**22.5 Gy** (33%)	within T	67.5 Gy/35 d	**19%** (64% vs. 45%**)	Yavuz [15]
e.	Bladder – Amsterdam	40 Gy/28 d	**(B_1)** – ERT	**15.0 Gy*** (27%)	within T	55.0 Gy/28 d	**10%** (55% vs. 45%**)	Pos [16]
f.	Nasopharynx, MGH, Boston	64 Gy/45 d	**(C_s)** – BRT-LDR	**15.0 Gy** (19%)	1 d	79.0 Gy/46 d	**27%** (86% vs. 59%**)	Wang [19]
g.	Nasopharynx, Rotterdam	60-70 Gy/42-49 d	**(C_F)** – BRT-HDR	**46x 3.0 Gy** (23%)	5 – 8 d	78.0-82.0 Gy/50-55 d	**20%** (86% vs. 56%)	Lavendag [20]
h.	Breast-EORTC 22881-10881	50 Gy/35 d	**(C_{ES})** – ERT/BRT-HDR	**16 Gy** (24%)	1 – 7 d	66.0 Gy/36-42 d	**3%** (96% vs. 93%)	Horiot [22]
i.	Breast – Heidelberg	50 Gy/35 d	**(C_s)** – BRT-PDR	**20 Gy** (29%)	1 d	70.0 Gy/36 d	**10%** (93% vs. 83%**)	Harms [21]
k.	Breast – ARCT – IORT	51 Gy/42 d p.op.	**(D)** – IORT	**8-9 Gy** = 18 Gy in 2 Gy fx (26%)	1 d	69.0 Gy/52 d	**17%** (100% vs. 83%**)	Sedlmayer [8]
l.	Rectum, Rome	45 Gy/35 d	**(D+H)** – IORT + CHT(c)	**15 Gy** + 5 Fu & Mtm–C	1 d	60.0 Gy/36 d + 5-Fu & MtmC	**33%** (91% vs. 58%)	Valentini [9]
m.	Head & Neck – DAHANCA 7	56 Gy/39 d	**(E)** – ERT	**10 Gy** in Sat's (15%)	within T	66.0 Gy/39 d	**10%** (67% vs. 57%)	Overgaard [3]
n.	Head & Neck – CAIR	54 Gy/40 d	**(F)** – ERT	**18 Gy** in Sat's and Sun's (18%)	within T	72.0 Gy/40 d	**42%** (73% vs. 31%)	Składowski [4]
o.	Head & Neck – SIB-IMRT	50 Gy (CTV)/35 d	**(G)** – IMRT	**10 Gy** (GTV) (17%)	within daily	60.0 Gy/35 d	– feaSIBle	Amosson [11]
p.	Brain – SIB–IMRT	56 Gy (CTV)/38 d	**(G)** – IMRT	**14 Gy** (GTV) (20%)	fraction time	70.0 Gy/38 d	– feaSIBle	Suzuki [10]
r.	Nasopharynx – Intergroup 0099	70 Gy/49 d	**(H)** – $CHT_{(C)}$	3 courses **Cis-pl + 5-Fu**	within T	70.0 Gy/49 d	**45%** (69% vs. 24%)	Al-Sarrat [23]
s.	Oral cavity	70 Gy*/40 d	**(H)** – $CHT_{(C)}$	2 courses **Cis-pl + 5-Fu**	within T	70.0 Gy/40 d	**25-30%**	Brizel [25]

[* – twice-a-day hyperfractionation; ** – historical control group; T – time of basic treatment; OTT – overall treatment time; MDACC – MD Anderson Cancer Center; ASCBRT – accelerated superfractionated radiotherapy; ABCT – Austrian Breast Cancer Trialists; SIB-IMRT – Simultaneous Integrated Boost-Dose Intensity Modulation; ERT – external radiation treatment; BRT – brachytherapy; LDR, HDR, PDR – Low-, High-, Pulse Dose; IORT – intraoperative radiotherapy; (C_s) – single dose brachytherapy; (C_F) – fractionated brachytherapy; $CHT_{(C)}$ – concurrent chemotherapy; Cis-pl – Cisplatin; 5-Fu – 5-Fluorouracil; Mtm-C – Mitomycin C]
* % reduction in recurrence rate RR = (recurrence rate A – recurrence rate B) A, thus RR overall = (7.3-4.3)/7.3=41%; RR young pts = 19.5-10.2/19.5=47%

Taiwan to treat nasopharyngeal cancer [17]. After a baseline dose of 45 Gy delivered through two opposed fields the boost of 25 Gy was given using 7-field IMRT. The results of the 7-field IMRT were superior to the results of the 5-field IMRT and 5-field 3D-Conformal RT. IMRT-boost produced dose distributions that better conform to concave targets. The pilot clinical study has proven this method feasible and clinical trials are ongoing.

Brachytherapy (BRT) boost as either a single shot or as a fractionated dose is one of the oldest and best recognized methods of the boost. It is widely used in many tumour locations. Usually it is applied immediately after completing the basic fractionated treatment using Low-, High- or Pulse-Dose BRT (Table I f,g,h,i). The advantage of such a boost-form is its delivery in one or a few days without much extension of OTT. Therefore the overall dose intensity significantly increases. On the other hand, an increased risk of local necrosis should be carefully weighed, especially when the boost-dose is not homogenously distributed and hot spots may occur. Wang [19] published the results of intracavitary LDR-boost of 15 Gy in a single fraction after 64 Gy in 45 days given to the nasopharynx showing consistently better local tumour control (gain of 31%) than external beam irradiation alone (ERT). However, some uncertainties may arise because such excellent results have never been reported again by any other authors. In Rotterdam, Lavendag et al [20] treating nasopharyngeal cancer used a protocol involving HDR-BRT boost of 4-6 fractions of 3 Gy after 60-70 Gy of ERT (Table Ig), and achieved a 20% higher LRC than in historical controls. Severe complications were uncommon.

In Heidelberg, Harms et al [21] have used 15-25 Gy of Pulsed-Dose BRT boost after conserving surgery and external radiotherapy for breast cancer patients at high risk of local recurrence (Table Ii) and they observed a gain in local control of 10%. Similar results were noted in a large multicenter EORTC trial – 228831-10881 (Table Ih) with a boost fractionated dose of 16 Gy [22]. The results demonstrate the "boost benefit" as a decrease in the recurrence risk from 7.3% to 4.3% ($p<0.0001$). The largest clinical benefit was observed in patients younger than 40 years (reduction of the local recurrence rate from 19.5% to 10.2%) but the ratio of reductions in recurrence rates were not different (41% and 47% respectively). In conclusion, the trial indicates that the boost of 16 Gy after whole breast irradiation to 50 Gy reduces local recurrence rates by about one-half and that, since younger women recovered more frequently, they were the ones who achieved the greatest absolute benefit.

Intraoperative radiotherapy (IORT) used prior to whole-breast irradiation is an interesting option for a single shot-boost. Sedlmayer et al [8] introduced IORT-boost as a part of conservative management of breast cancer including conservative surgery and ERT of 51-56 Gy in 42 days. After tumorectomy the tissue surrounding the excision cavity was treated with IORT of 9 Gy applied to the 90% reference isodose using electrons. Whole-breast ERT was performed after wound healing. IORT boost of 9 Gy is biologically equivalent to about 18 Gy given in 2Gy fractions. During the median follow-up of 26 months (14-41 months) no in-breast recurrences have been observed. It is too early to evaluate this method, but compared with other boost methods IORT has some advantages, e.g. first of all – it guarantees an accurate dose delivery, secondly – it allows complete skin sparing and less late effects (fibrosis) may be expected than after brachytherapy HDR-boost. Finally, IORT prolongs the surgical procedure by only 20-30 minutes, while whole combined treatment time can be shortened by 1-2 weeks. IORT became an integrated modality in breast conserving treatment in Salzburg with over 500 patients treated since 1998.

It is quite well recognized that a combination of chemotherapy and radiation tends to maximize the anti-tumour effect. Concurrent chemo-radiation has been shown to improve local control and survival in several types of tumour. Concurrent chemotherapy can be considered as another form of boost (CHT_C). The CHT_C boost combined with modest-dose radiation produces a LTC gain higher than high-dose radiation therapy. In the Catholic University of Rome, Valentini [9] combined two different forms of boost in the treatment of patients with locally advanced (T4) rectal cancer (Table Il). Preoperative ERT of 45 Gy in 35 days was combined with "chemo-concomitant-boost" of 5-Fluorouracil (96 h continuous bolus of 1000 mg/m^2/day in week 1 and 4) and Mitomycin C (10 mg/m^2 bolus in day 1). This "chemo-boost" was repeated in the last week of the ERT. After 6-8 weeks patients underwent radical surgical resection with IORT-boost of 15 Gy to the tumour bed. The actuarial 5-year loco-regional control rate was 33% higher than for regular chemo-radiation combined with surgery (91% vs. 58%). No late toxicity related to IORT was detected in the median follow-up time of 3 years. This combined boost seems to be most beneficial to patients undergoing complete resection, as compared with partial resection only. The Rome group has noted a very high rate (85%) of sphincter preservation.

The Rome results are consistent with those from various US centres (i.e. Massachusetts General Hospital in Boston, MD Anderson Cancer Center in Houston). Moreover, the Gastrointestinal Tumour Study Group found that the combination of ERT with concurrent chemo-boost and IORT is more effective in the treatment of resectable pancreatic cancer than the combination of surgery, postoperative ERT and concurrent chemo-therapy. The incidence of local failure was 3-times lower (17.6% vs. 51%). Perioperative morbidity and mortality rate recorded in the Rome series was similar to that observed in other series without IORT.

Although the results of concurrent CHTC might be considered controversial, a few recent trials have demonstrated an improvement in the LRC of head and neck cancers. Apparently convincing evidence came from the Intergroup 0099 trial [23]. In that study (Table Ir) patients with nasopharyngeal cancer were randomly assigned to concurrent chemotherapy with ERT of 70 Gy

in 46 days vs. ERT alone. Cis-platin of 100 mg/m^2 was delivered on days 1,21 and 42 of ERT, followed by 3 courses of adjuvant Cis-platin and 5-Fluorouracil (1000 mg/m^2/day on days 1-5). The trial was stopped early because of a highly significant 3-year disease-free survival benefit of 45% (69% vs. 24%). The major criticism is that the results in the control group were poor. However, Cooper et al [24] reported recently a 3-year survival of 93% for patients with stage III and IV nasopharyngeal cancer treated with a regimen similar to that used by the Intergroup. Tumour control improvement (32%) remained high (93% vs. 61%). In contrast, using chemotherapy as neoadjuvant treatment prior to radiation did not show a pronounced gain in two different phase III trials in MDACC and in Prince of Wales Hospital in Hong-Kong. The authors try to explain the lack of the LTC gain as resulting from inadequate intensity of neoadjuvant CHT.

Therapeutic benefit for oral cavity after concomitant boost is well documented by MD Anderson Cancer Center studies [2]. Further increase of such benefit in local control by 12–17% (to about 30%) was noted by Brizel et al [25], who delivered 70 Gy in 1.25 Gy fractions given twice-a-day in 40 days, plus a concurrent chemo-boost of Cis-platin and 5-Fluorouracil during week 1 and 6 of irradiation. The benefit in loco-regional control strongly correlated with improvement in disease-free and overall survival.

A scattergram of gains in local tumour control (LTCG) based on the present analyses of the results of different "boost" forms does not establish a single and simple correlation between LTC gain and the boost dose (Figure 2). It can only be deduced that above 10 Gy and up to the limit of 25 Gy of boost dose given in 2 Gy fractions, 1 Gy increase in dose may, on average, produce approximately a 1–1.5% gain in the LTC. This uncertainty regarding the therapeutic benefit arises from a large heterogeneity of tumor types, sizes and locations, which are reviewed, and also from variations in boost intensity and techniques of delivery. Clinical and biological heterogeneity of tumours, together with dose nonuniformity within the target volume, suggest that great caution should be exercised in interpreting the results. The benefit

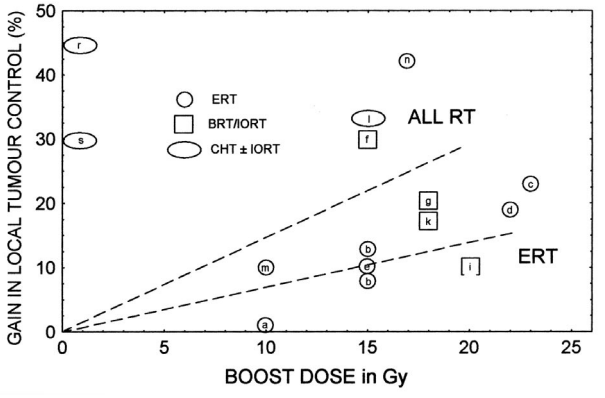

Figure 2. Scattergram of therapeutic gain in local tumour control (≥3 yrs.) depending on boost dose. (Letter abbreviations are taken from Table I)

expected from raising the dose in the boost volume is very non-linear and may only slightly increase the Tumour Cure Probability (TCP), whereas a small volume under-dosed can entirely prevent a cure. The biological impact of a boost-dose depends not only on the magnitude of boosting, but also on its size and relative volume involved.

The present review shows that external radiotherapy, although widely accepted, has limited "power", and different forms of boost may produce a higher gain in local tumour control. On the other hand, the traditional time for boosting immediately after completing the basic course of irradiation and the dose fractionation pattern of the boost are not the only solution. Single shot-boost can be used at the beginning of treatment or even a few days before as an intraoperative boost. Further combinations are offered by chemo-boosts. The studies presented suggest that chemotherapy combined as a boost with radiation significantly enhances the tumour benefit, at least in head and neck and rectal cancer. A recent review from the Mayo Clinic in Rochester [26] shows, that rectal cancer is of special interest. The rationale for using chemo-radiation is based on the risks of relapse after surgery alone, on evidence of radioresponsiveness to primary or preoperative irradiation, and on the facilitation of sphincter preservation as a result of tumour "downstaging/downsizing". The Gastrointestinal Tumour Study Group trial (GTSG-7180) and North Central Cancer Treatment Group trial (NCCTG 864751) both show a significant improvement in local tumour control and disease-free survival and a decreased incidence of distant metastases, from using a concurrent, protracted low-dose 5-Fu schedule instead of a concomitant boost of 5-Fu as a bolus.

The present review leads to the conclusion that no single most effective boost schedule can be chosen. Evolution of a single-boost modality into a two-or-three component boost policy in which chemotherapy plays an important role can be observed. The role of ongoing and future studies is to define which boost schedule, time of delivery, sequence and size of boost target volume can produce optimal therapeutic benefit for specific tumour types, sizes and locations.

When is a boost really a boost and when it might work?

Fletcher's original definition can be simplified to say – a boost is an extra dose given to a target subvolume. The answer to whether it is necessary or beneficial could be – yes it is, but it could also be – no it is not. Such a dilemma arises from the original definition still commonly used, which does not specify the essence of the boost, which is to increase local tumour control probability (TCP). This immediately places "boosting" into the field of clinical radiobiology. A large family of clinical dose-response curves for tumour control probability (TCP) are generally shallow and reflect heterogeneity in tumour and treatment characteristics, such as differences in intrinsic radioresistance, number of clonogens, rate of repopu-

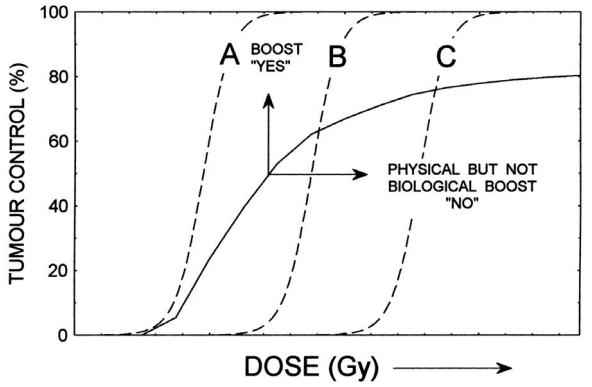

Figure 3. Theoretical TCP curves for biologically heterogeneous population of tumours of the same size, site and stage comprised of subpopulations "A", "B" and "C" of very sensitive, moderately sensitive and resistant tumours (modified from Thames et al, 27)

lation, acute or persistent hypoxic fraction and variations in dose fractionation patterns. In the early nineties the problem of the TCP-dose escalation relationship has been discussed by Thames et al [27]. The authors considered a heterogeneous population of tumours with a representative shallow TCP curve (Figure 3), comprised of three equally sized subpopulations of very sensitive (A), moderately sensitive (B) and resistant (C) tumours. An increase in the dose that will achieve an average of 50% control in an equal mixture of the three tumour groups will not affect the probability of cure of sensitive (A) tumours because they will be directly, nearly certainly, controlled by that dose. In contrast, tumours in "C" group are resistant and failure remains practically certain with a modest dose escalation. Therefore, dose escalation above the "average" dose for 50% control of a mixture of the A B and C tumours may change the TCP of B tumours only. Zagars et al refer to this subpopulation as the stochastic fraction [28], where local control is determined to some extent by chance. The outcome for this group is not fully predictable and the probability of control is a steep function of dose around the average TCD_{50}. According to Thames, the majority of clinical trials with unselected patient populations may fail to detect the benefit of a modest (e.g.10%) dose escalation but it does not mean that it may not be a good strategy.

Tumour radiosensitivity is not the only item in a consideration of "boosting". Accelerated repopulation with the speed increasing toward the end of week 5-7 of conventional irradiation may, likely, neutralize the effect of each extra dose delivered in a multifraction regimen given after completing the baseline course of ERT (Figure 3 – horizontal line "no"). Therefore, the physical dose is boosted, but the biological dose is not, and such an extra dose is completely wasted. The problem of accelerated clonogen regrowth can be counterbalanced by boosting the dose with minimal or no extension of overall treatment time (Figure 3 – vertical line "yes"). This can be achieved by single-shot BRT, concomitant boost delivered as a second daily fraction during the main course of ERT (e.g. in last 2 1/2 weeks), concurrent chemo-boost or by Simultaneous Integrated Boost using IMRT (Figure 4). In all these regimens OTT is not significantly prolonged and can even be shortened. This is not a theoretical concept, but evidence-based. The results of the RTOG 83-13 trial [12], discussed earlier, convincingly show that dose escalation with extension of overall treatment time may gain nothing. A similar relationship was observed by Suwiński et al [29] for postoperative radiotherapy (Figure 5). The results show that the increase in dose with extension of OTT produces no gain in the TCP, but that a higher dose with no increase in OTT is beneficial for TCP. On the other hand, the authors suggest that the difference in the effect of protracted vs. shortened OTT is an intrinsically non-linear relationship between OTT and TCP: there is less gain in TCP by shortening OTT by a few days than what can be lost due to protraction of OTT over the same number of days. They also have noted

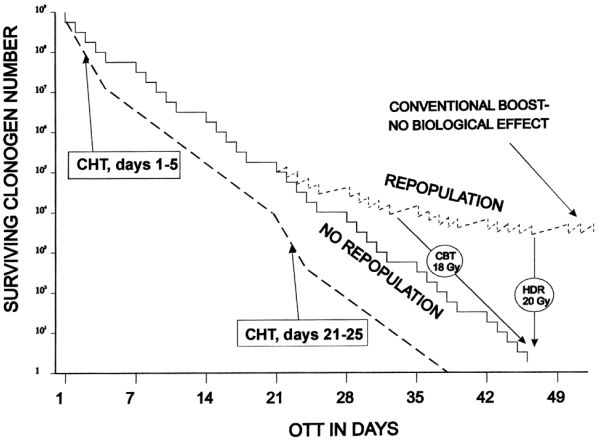

Figure 4. Model cell survival curves for a tumour with 10^{10} cells treated with 70 Gy in 2 Gy fraction with D_{10}=7 Gy: (D_{10} is the dose decreasing cell survival by one decade). This example shows that when a conventional boost of even 20 Gy in 26 fractions is administrated after completing the ERT, when repopulation is the most rapid, it can counterbalance cell-killing and no biological gain can be expected. The boost may become effective by delivering it as a single shot BRT, or by a concomitant boost (CB) in the last 2 1/2 weeks of treatment or by concurrent chemo-boost during ERT

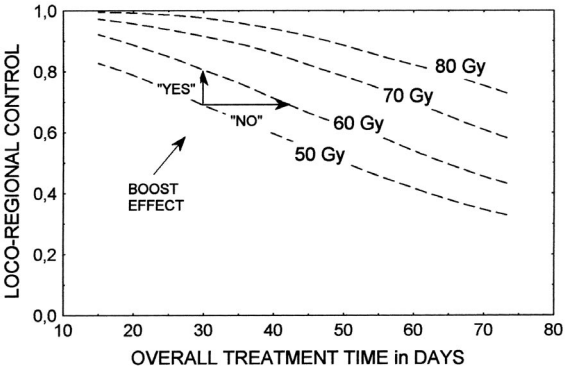

Figure 5. Relationship between reduction in locoregional failure probability, total dose and overall treatment time for postoperative radiotherapy of head and neck cancer. "Horizontal" dose escalation with OTT extension is NOT a boost because the effect of the extra dose is neutralized by regrowth of surviving tumour clonogens. "Vertical" increase in dose intensity – YES, is a boost (Suwiński et al, 29)

that an increase in dose intensity from 9 Gy/week to more that 10.5 Gy/week resulted in an increase 5-year LTC by 15%. Thus, boost efficacy is not only a matter of the size of extra dose, but also a matter of the time taken for its delivery. This leads to two terms: *dose escalation* and *dose intensity*, which are often misinterpreted. The first term simply means an increase in physical dose whereas the second one defines how many Grays are delivered per unit of time (hour, day, week).

Consequently, dose escalation may or may not have a biological impact whereas dose intensity does. Following Fletcher's intuition, dose escalation with time extension is not a boost in the biological sense. The role of a boost is to increase dose intensity (DI) by giving extra dose with little or no increase in OTT. If the basic treatment is for example 60 Gy in 42 days, and the planned boost dose is 16 Gy, then its delivery in a standard fractionated manner needs an extra 10-11 days. For such treatment the basic DI is 1.43 (60/42 Gy/day) and, an extra 16 Gy in 11 days does not change the DI (76/53=1.43). Therefore, this is not a true boost in the tumour undergoing a rapid regrowth in its clonogen number. But if 16 Gy can be delivered in only one extra day, then the DI will increase to 1.77 (76/43 Gy/day) and this is a real boost for rapidly growing tumour clonogens. Therefore, boost means an increase in dose intensity in a biological sense, but not necessarily dose escalation. However, this is still only a tool of the boost, but not the essence of the matter. When planning and delivering a boost an extra cell kill is expected. The battle concentrates on a few tumour clonogens, which survive a series of basic fractions with the aim of killing them all. When an average 1 to 3 cells survive, the TCP for the individual patient is between 37% and 5% ($e^{-1} \rightarrow e^{-3}$). An extra dose of 1 x D_{10} added to the dose which reduces cell survival to an average of 1 clonogen per tumour will decrease the surviving fraction by one decade to an average 0.1 cell/tumour which will result an increase in the TCP from 37% to 90%. This 53% gain in local tumour control probability reflects a *"real biological boost"*. The size of the extra dose and the boost volume are only tools to achieve the goal and a more appropriate term for an increase in "biological" dose, as distinct from "physical boost" could be "burn down boost".

How large should a boost dose and boost volume be?

The biological impact of "effective" boost depends non-linearly not only on the magnitude of the increase in dose (size of boost) but also on its timing and boost volume [30, 31]. For tumours which accelerate the growth rate of surviving clonogens late in the treatment an increase in TCP can only be expected when OTT is kept as short as possible. When subclinical tumour cell deposits are a factor in treatment planning (elective or postoperative boost) it should also be shortened, because rapid growth is an inherent characteristic of small tumour deposits and is occuring at the beginning of treatment, without the lag period that characterizes the response of primary bulky tumours.

When considering the size of the boost dose and volume it is no longer mandatory to deliver a uniform dose to whole target volume. Non-uniform dose distribution is almost unavoidable in brachytherapy and stereotactic radiotherapy and it is not a disadvantage. Selective delivery of a higher dose to subvolumes of the target can lead to either a small and clinically undetectable increase in tumour control or a substantial increase, depending on how large is the extra dose and is it encompassed with the boosted subvolume. It is commonly thought, that tumour cell density increases towards the center of the tumour, but on the contrary the number of clonogens is proportional to tumour volume, and so because the volume is proportional to the cube of tumour diameter, most clonogens are in the outer part of a tumour cross-section. Thus, it is unreasonable, and even risky, to assume that any part of the edge of the CTV might have fewer cells. The PTV, however, can be shrunk to define the size of the boost volume. Although CT, MRI, PET and biochemical or molecular imaging can show regions of higher cell density, hypoxia or rapid repopulation, primary or elective boost geometry is still subjective. Considering non-uniform dose distributions, a single tumour or subclinical deposit can be presented as a conglomeration of a number of subvolumes.

Moving from theory to practice there are at least two subvolumes, i.e. large basic PTV for the baseline course of irradiation and a smaller one, within the large, for a boost. Overall TCP resulting from delivery of baseline dose to large volume and extra boost dose to smaller subvolume will be a function of two different TCP's which can be calculated from the equation:

$$TCP_T = TCP_i \times TCP_B \qquad \text{(a)}$$

thus,

$$TCP_T = e^{-[N * \{(1 - V_B) * SF_{2.0}^{D_i/2.0} + V_B * SF_{2.0}^{D_B/2.0}\}]} \qquad \text{(b)}$$

where N is initial number of tumour clonogens, V_B is relative subvolume of boost, $SF_{2.0}$ is an average surviving fraction after 2.0 Gy fraction, D_i is baseline dose and D_B is boost dose. This equation is explained in detail in Appendix 1. This could be easily rewritten using $_{eff}D_o$ or D_{10} instead of $SF_{2.0}$ but it will not change TCP_T quantitation.

Using equation (b) and the method proposed by Withers (30), Tome and Fowler [31, 32], improvement in overall TCP_T was calculated depending on the baseline TCP (standard regimen if not boosted), the size of boost dose and boost volume relative to the primary GTV. It is obvious that the maximum increase in TCP can be expected when the whole PTV would be included in homogenously escalated dose volume.

Table II. Therapeutic gain in local tumour control (LTC) depending on the size of boost dose and boost volume in relation to the level of the baseline TCP**

BOOST VOLUME**** ⇒	TCP increase by percentage points*					
	10%		50%		80%	
Boost dose in D_{10}	1 x D_{10}	2 x D_{10}	1 x D_{10}	2 x D_{10}	1 x D_{10}	2 x D_{10}
Baseline TCP***						
10%	3%	3%	17%	20%	42%	50%
50%	3%	3%	17%	19%	32%	36%
90%	2%	2%	4%	4%	7%	8%

* Therapeutic gain in LTC is calculated as an increase in percent points from the baseline TCP (basic treatment to whole PTV) to overall TCP accounting the effect of boost

** D_{10} is the dose reducing cell survival by an average of one decade and for the present calculation D_{10} of 7.0 Gy was used

*** Baseline TCP is calculated for whole PTV irradiated with a homonogenous dose

**** As a percentage of tumour volume

Table II shows that a boost is not very effective when the baseline TCP is already high, e.g. 90%, and/or it is delivered to a small boost volume. Boost efficacy in such a case is theoretically worthless. An exception is if hypoxic cells are present in the boosted volume. Independently of how large is the boost dose the results in Table II suggest that overall TCP is essentially determined by the percentage of tumour volume in which the dose is not escalated. Once the boost dose is applied to a volume larger than 50% of the GTV, gains in the TCP increase more steeply, especially when the baseline control rates are low. For example, if a dose producing TCP of 50% was boosted throughout 50% of the GTV by 1 x D_{10} the TCP would increase by 17% (from 50% to 67%); but if the boost volume was enlarged from 50% to 80% of the GTV, the TCP would increase by a further 26%, up to 93%. Increase in the boost dose itself, e.g. from 1 x D_{10} to 2 x D_{10} within the same boost volume does not produce substantial improvement in the TCP.

Figure 6A shows that boost dose above 12–16 Gy does not produce a significant further increase in the TCP and respective boost curves are almost identical in the range 18–30 Gy. Tome and Fowler [31] demonstrated that beyond a boost dose ratio (bdr) of 1.2–1.3 the curve for TCP reaches a plateau unless hypoxic cells are a problem. The bdr is a ratio of dose in the boost volume to the preboost dose received by the remainder of the GTV.

For the present calculations "effective" D_{10} of 7 Gy was taken from tumour cells assayed *in vitro*. However, Withers [29] postulates that retrospective analyses of clinical results produce a relatively shallow slope of most TCP curves because of the heterogeneity of human tumours in the factors determining radiocurability, and heterogeneities of dose prescription and distribution. This implies an effective D_{10} close to 20 Gy for a regimen of 2 Gy fractions. On the other hand, for single–dose brachytherapy or radiosurgery of 18–20 Gy the D_{10} value would be approximately 2.5–3.0 Gy. It may explain why brachy-boosts have been found more effective than the conventional ERT boost given in 2 Gy fractions (Table I).

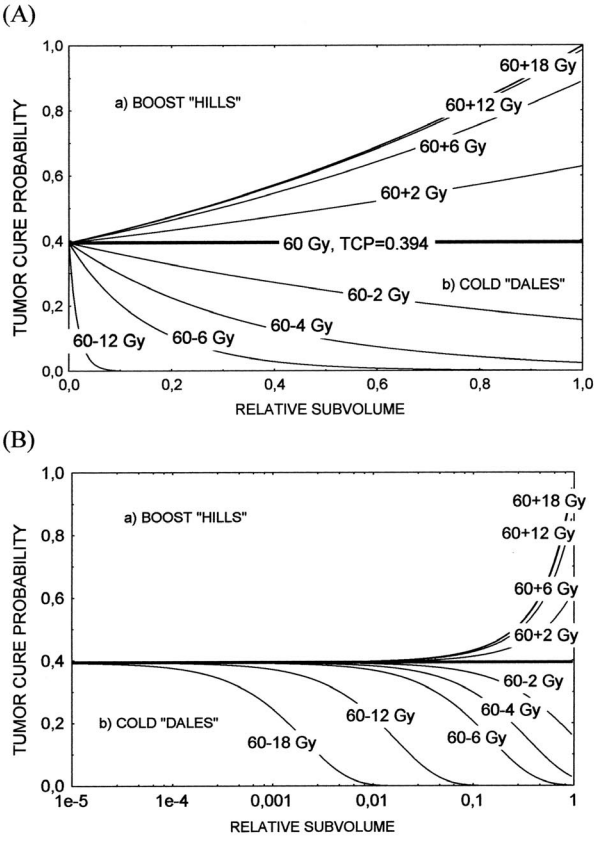

Figure 6. Plots of the estimated increase or decrease in TCP as a function of over- or underdosage and the size of subvolumes involved. Subvolume coordinate is presented (A) in linear scale; (B) in log scale. Regimen of total dose of 60 Gy homogenously delivered in 30 fraction in 42 days is assumed as a standard. Assuming initial number of tumour clonogens $N=10^9$ and $SF_2=0.5$ estimated TCP is 0.394. Parameters N and SF_2 are held constant and changes in TCP were calculated for changes in total dose and in the size of subvolumes receiving the boost-dose or underdosage, using equation (6) presented in Appendix 1 in detail

A basic limitation for the concept of tumour boosting is the risk of necrosis of normal tissue within the PTV, but very high boost doses can be avoided because there is no need to exceed "bdr" of 1.3 to obtain maximum increase in the TCP.

Hills and dales

Discussing advantages of boosting it has to be pointed out that tight conformation boost field (volume) to the margins of gross tumour mass increases the risk of geographic underdosage. The consequences of geographic underdose depend upon how many tumour clonogens are relatively underdosed, and how large is the magnitude of the underdosage. Figure 6A-(b) shows a dramatic decline in TCP for small underdosed volumes of <20%, but the absolute decline in TCP is influenced by the magnitude of the underdosage. If only 20% of the tumour were underdosed by 0.5 x D_{10} (3.5 Gy) TCP would decrease by 10% but if as little as 5% of target volume would receive a dose decreased by 12 Gy the TCP will decrease almost to zero (Figures 6A, B).

Figure 6A shows that the TCP curve for underdosage of a 60 Gy minus 12 Gy is much steeper than that for the increase by 12 Gy. This is illustrated even more clearly in Figure 6B, where the coordinate of "boosted" or "missed" volume is presented in a log scale. A high dose deficit even in a small subvolume is more likely to lead to failure of treatment than a high dose boost delivered to a relatively larger subvolume is to lead to benefit. Therefore small dales (Figure 7A) are more dangerous than large beneficial hills (Figure 7B). A dose deficit larger than 20% of the prescribed dose to 1% volume of GTV may lead to serious loss of TCP, even if 80% of the target receives a 10% boost. Assuming TCD_{40} of 60 Gy (Figure 6) a "dale" of 12 Gy in volume of 1% ruins the whole potential benefit of the boost, even if 80% of the GTV receives a 20–30% boost. Practically, a dose deficit larger than 20% in only 1% essentially reduces TCP to zero (Figure 7A). A dose-dale becomes hazardous when there is a 10% deficit in more than 10% of the tumour volume. Planning to increase LTC gain by giving a boost, one should keep in mind that any underdosage within the target volume is a more critical and powerful determinant of treatment outcome than optimal boost dose delivered to the defined subvolume. Dose escalation in small volumes of the tumour, regardless of its magnitude, is of little value in any situation, whereas a large dose deficit in a very small volume is a disastrous for local tumour control.

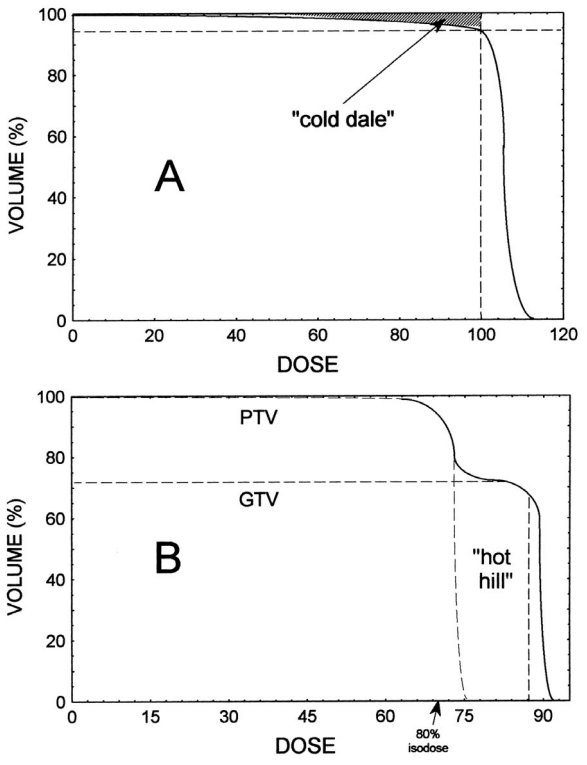

Figure 7. Dose volume histograms for conformal radiotherapy with "cold dale" (A) and "hot hill" (B)
(A) DVH follows the specification "full prescribed dose to 95% of the tumour volume", but the long tail-back shoulder (cold dale) illustrates 50% dose-deficit in 1% volumes and 30% deficit in 2% volume. Such "cold dale" completely ruin not only the potential benefit of a boost, but in the example shown, they eliminate any chance of tumour control (B) SIB planning with 80% isodose encompassing PTV provides at least 25% increase in physical dose within GTV (boost hot-hill) illustrated in the DVH by the vertical tail. The size of the "hot-hill tail" corresponds with the size of boost and subvolume involved

Optimal "burn down" – boost

As discussed above, a boost dose delivered in a prolonged overall treatment time is an escalation of dose but is not a boost as to the biological effect in tumours such as squamous cell carcinomas of the head and neck, in which clonogens regenerate rapidly late in the course of treatment. Such a "boost" may only increase the risk of late normal tissue injury. Among ERT solutions, concomitant boost with no extension of OTT is commonly used, but its efficacy is lower than expected. A single-dose shot of BRT or IORT is likely to be more effective. Recently, concurrent chemo-boost combined with BRT or IORT boost has began to look promising. However, conformal radiotherapy with heterogeneous dose distributions, using dose intensity modulation, seems to be an optimal resolution. Steep gradients in dose distribution permit a higher dose per fraction within gross tumour mass than is possible with standard therapy, and also allow a lower dose to the peripheral volumes of PTV (Figure 7). Therefore, within each daily fraction exposure the dose intensity to the tumour can be selectively increased. This form of Simultaneous Integrated Boost (SIB) can be used for the whole course of treatment or as a technical boost during the second half or one third the course of irradiation: the treatment may begin as standard dose distribution and then the dose intensity to the tumour can be selectively increased.

Such complex beam arrangements produce steep dose gradients. For example, if the whole tumour is encompassed at the 80% isodose, and 70 Gy in 7 weeks is prescribed to the PTV, the dose per fraction within the tumour will increase by a factor ranging up to 1.25 (100/80) and the total dose would range between 70 Gy and 87.5 Gy resulting in acceleration of dose intensity up to 25% (Figure 7B). Obviously, dose intensity could be further increased by prescribing the dose to a lower percent rate isodose. Furthermore, the higher dose per fraction yields an increase in the biological dose

depending on the α/β value. Many tumours currently treated with conformal therapy have a relatively slow proliferation profile (e.g. prostate, meningiomas, chordomas). If such tumours are characterized by a low α/β value of 2.0 Gy and if the fraction dose is 2.5 Gy, compared with 2.0 Gy in the remaining part of PTV, then the 25% increase in physical dose would be amplified by a further 12.5% and the biological dose within the GTV would be 37.5% higher than the dose in the remaining PTV. However, it has to be remembered that any increase in dose intensity in only a small volume of the tumour will not improve therapeutic gain, independent on the type or magnitude of the boost used. The old rule of thumb is that not more than 10% less dose in not more than 10% of the target volume is not bad, but according to Tome and Fowler [32], it conceals the highly asymmetrical nature of such a guideline. The DVH can correctly demonstrate the full prescribed dose to 95% of the tumour volume, but the long tail-back (Figure 7A), not always readily visible in the DVH but representing a 50% dose deficit in 1% volume, will reduce TCP to zero. Thus, prescription of a 100% dose to 95% of the target volume is not safe enough, because it permits as much as 5% of the tumour volume to be underdosed to a possibly dangerous degree. To avoid such a risk of small cold dales and to achieve the expected benefit of boost dose, planning should be performed carefully and precisely. It also indicated that other constraints are needed, such as a minimum target dose or requiring that the tumour EUD (Equivalent Uniform Dose, i.e. equal total cell kill) should not be smaller than the prescribed tumour dose. Finally, in order to achieve the effect of burn-down boost (optimal TCP benefit), the size of the boost dose should be tailored to the number of decades of the surviving tumour clonogens expected to be killed by the boost.

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Appendix 1

Tumour cure probability (TCP) is exponential function of an average number of the survived tumour clonogens (x):

$$TCP = e^{-x} \tag{1}$$

where x=N∗SF, and an N is initial number of tumour clonogens. SF is surviving fraction and for fractionated regimen "i" SF_i can be calculated from:

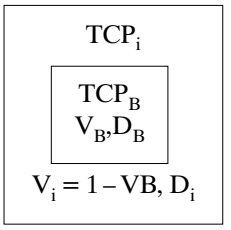
$$SF_i = SF_{2.0}^{(D_{i/2.0})} \tag{2}$$

where $SF_{2.0}$ is an average surviving fraction after 2.0 Gy and D_i is a total dose for regimen "i".

Using equation (1) and (2), TCP equals:

$$TCP_i = e^{-[N \cdot SF_{2.0}^{(Di/2.0)}]} \tag{3}$$

If boost dose D_b is delivered to subvolume V_B which is a part of target volume, i.e. PTV_i(Vi) then V_B receives total dose D_B which is a sum of the baseline dose and an extra boost dose:
$D_B = D_i + D_b$ and it is delivered to
relative boost subvolume $V_B = V_b/V_i$ which reflects respective proportion of initial number of tumour clonogens. Consequently the remaining subvolume of PTV receiving only baseline dose is



$$V_i = 1 - V_B$$

Because both subvolumes contain different initial number of clonogens irradiated with different total doses D_i and D_B, the TCP for these subvolumes will also be different and overall TCP_{total} equals:

$$TCP_{total} = TCP_1 * TCP_B \tag{4}$$

Using equation (3) and (4) overall TCP equals:

$$TCP_{total} = e^{-[N*(1-V_B)\cdot SF_{2.0}^{Di/2.0}]} * e^{-[N*V_B \cdot SF_{2.0}^{DB/2.0}]} \tag{5}$$

$$TCP_{total} = e^{-[N*\{(1-V_B)\cdot SF_{2.0}^{Di/2.0} + V_B \cdot SF_{2.0}^{DB/2.0}\}]} \tag{6}$$

Example: After baseline dose (D_i) of 60 Gy given to whole PTV containing 10^9 cells it was decided to delivered a boost dose of 9 Gy to 90% of the PTV volume. If surviving fraction after 2 Gy is $SF_{2.0}$ = 0.5 what would be overall therapeutic benefit in the TCP?

Solution: For 60 Gy in 30 fraction (D_i) without boost the TCP calculated using equation (3) is

$$\begin{aligned} TCP_{standard} &= e^{-(10^9 * 0.5^{60/2})} \\ &= e^{-0.931} \\ &\cong 39\% \end{aligned} \tag{7}$$

After boost schedule parameters are as follows:

$N = 10^9$	D_B = 69 Gy
D_i = 60 Gy	V_B = 0.9
V_i = (1-0.9)=0.1	$SF_{2.0}$ = 0.5

Using equation (6) TCPtotal would be:

$$\begin{aligned} Ln\,TCP_{total} &= -[10^9 * (0.1 * 0.5^{60/2} + 0.9 * 0.5 \times 10^{69/2})] \\ &= -[10^9 * (0.9313 * 10^{-10} + 0.3704 * 10^{-10})] \\ &= -[10^9 * 0.1301 * 10^{-9}] \\ &= -0.1301 \end{aligned} \tag{8}$$

$$TCP_{total} = 0.878 \tag{9}$$

Answer: By giving 9 Gy boost to 90% of the PTV overall TCP increases from 39% to 87.8%, then therapeutic gain is 48.8%