

# The impact of cervical (GTV<sub>CRX</sub>) and parametrial (GTV<sub>LP</sub>, GTV<sub>RP</sub>) volumetric status on efficacy of radiotherapy for uterine cervix cancer in stage IIB and IIIB

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**Introduction.** The impact of volumetric staging of cervix and parametria on treatment outcome after combined BRT and IMRT of 135 cervix cancer patients in stage IIB and IIIB is analysed.

**Material and methods.** Cervical GTV<sub>CRX</sub> and parametrial (GTV<sub>LP, RP</sub>) volumes are subdivided into four subgroups. BRT with 30 Gy in three fractions was combined with IMRT 48 Gy in 24 fractions. For GTV<sub>CRX</sub> ≤ 35 cm<sup>3</sup> 5-year local control (LC) was 100%, which decreased to 87% for GTV<sub>CRX</sub> ≥ 130 cm<sup>3</sup>.

**Results.** Cervix and parametrial local recurrence were not higher than 3%. Major failures were periaortal nodes metastases (PNM) occurring during 5-year follow-up. Dose of ≥ 60 isoGy<sub>2,0</sub> effectively prevented the PNM. Underdosage < 55 isoGy<sub>2,0</sub> (GTV<sub>RP</sub>) resulted in an increasing PNM from 7% to 53%, strongly correlated with enlarging GTV<sub>CRX</sub> from 5 cm<sup>3</sup> to > 130 cm<sup>3</sup>.

**Conclusion.** Although cervix and parametria volumetric status are highly heterogeneous, they turned out to be better prognostic predictors than traditional TNM grading.

**Key words:** cervix cancer, volumetric staging, radiotherapy outcomes

## Introduction

Uterine cervix cancer in the stage IIB or IIIB (FIGO) develops in about 50–60% of patients and in about 25% of them periaortal lymph nodes metastases develop during 5-year follow-up [1, 2]. The EMBRACE trial [2] has shown interstage overlapping of parametrial involvement in stage IIB and IIIB, and intra-stage heterogeneity. Brachytherapy (HDR) combined with external irradiation (3D-IMRT) are used as a standard treatment modality. Traditional end-points are locoregional control, incidence of local recurrence, disease-free and overall survival, referred to as rank FIGO stages. On the contrary to head and neck cancer [3–10], volumetric sta-

tus has been incidentally explored as predictive and prognostic factors in radiotherapy for cervix cancer, although Magee et al. [12], Tsang et al. [13], Dubben et al. [3] clearly documented its importance. Doubling time (T<sub>pot</sub>) and cervix volume have been found major significant predictors for disease-free survival. These observations were strongly supported by Ito et al. [21]. These findings lead us to quantify volumes of the cervix (GTV<sub>CRX</sub>), and involved left and right parametria (GTV<sub>LP</sub> and GTV<sub>RP</sub>) and to analyse its impact on local cervix (LTC) and parametrial control (PTC), the risk of local recurrences, and on development of the periaortal lymph nodes metastases during follow-up, as well.

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## Material and methods

This retrospective study consists of 135 consecutive patients with IIB (26%) and IIIB (84%) cervix cancer treated during 2002–2008 in a single institution. The median age was 62 years (33–82 years). Using frequent serial CT scans, cervix volume (GTV<sub>CRX</sub>) and volumes of both, left and right parametria (GTV<sub>LP</sub> and GTV<sub>RP</sub>) were contoured and counted (fig. 1).

All patients were treated with hypofractionated HDR brachytherapy (BRT) using 30 Gy in three fractions combined with 3D-IMRT 48 Gy in 24 fractions. Majority of patients also received concurrent chemotherapy (cisplatin one-a-week) during radiotherapy. Overall treatment time ranged from 46 to 51 days. Follow-up was at least 5 years.

All data was subdivided into four groups (A–D) according to the cervix (GTV<sub>CRX</sub>) and parametrial volumes (GTV<sub>LP</sub> and GTV<sub>RP</sub>) (tab. I).

Brachytherapy of 30 Gy was hypofractionated, whereas EXRT with 48 Gy was delivered in conventional 2.0 Gy fractions. Physical doses of the HDR and EXRT should not be simply added, and therefore they were normalised to biologically isoeffective doses EQED<sub>2.0</sub>, if given in 2.0 Gy fractions, using formula [14, 15, 16]:

$$EQED_{2.0} = TD_{EXRT} (d_i + \alpha/\beta) / (2.0 + \alpha/\beta) + TD_{HDR} (1 + d_i/\alpha/\beta)$$

where TD is a total physical dose,  $d_i$  is dose per fraction and  $\alpha/\beta$  equals 10 Gy. For cervix total EQED<sub>2.0</sub> ranged from 108 to 115 izeGy<sub>2.0</sub>, and 47–67 izeGy<sub>2.0</sub> for each parametrium. Parametrial EQED<sub>2.0</sub> were estimated at the midline of each parametrium. Generally, the EQED<sub>2.0</sub> doses, for the right parametrium were unexpectedly lower (47–55 izeGy<sub>2.0</sub>) than those for the left one (50–67 izeGy<sub>2.0</sub>).

The relationship between GTV<sub>CRX</sub>, GTV<sub>LP</sub> and GTV<sub>RP</sub> and treatment outcomes was estimated using the following end-points:

- local cervix and parametrial control and incidence of local recurrence;
- incidence and time of occurrence of the periaortal lymph nodes metastases (PAM);
- EQED<sub>2.0</sub> doses vs. local control (LTC) of the respective GTV targets and PAM.

Dose-effect relationships were estimated using Shapiro-Wilk, Kaplan-Meier tests and Cox regression analysis. The significance of the results was estimated by a t-Student test modified by Yates, and  $p = 0.05$  was accepted as the significance level.

## Results

### Cervical and parametrial local control – distant failure

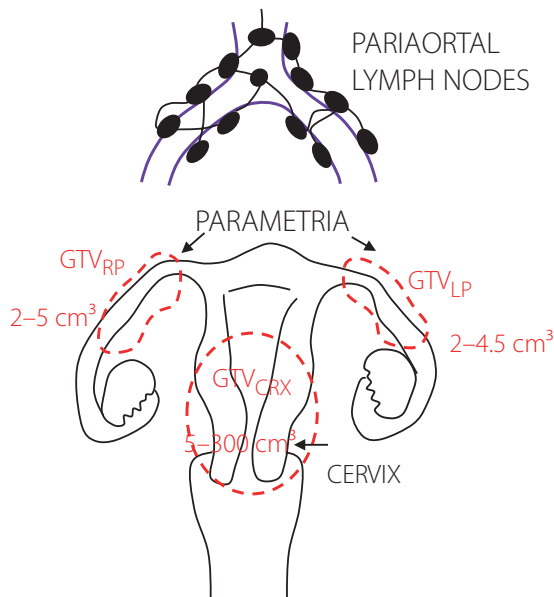
Histogram of local control recurrences and the PAM as a function of cervical and parametrial GTV and the respective EQED<sub>2.0</sub> are shown in details in appendix 1 (A–D). Overall 5-year LTC for the cervix cancer was 97.8% and 95.6% for involved parametria (tab. II).

For the GTV<sub>CRX</sub> up to 35 cm<sup>3</sup> (gr. A) no cervical and parametrial failures occurred. For the GTV<sub>CRX</sub> (gr. C) in the range 44–74 cm<sup>3</sup>, local or parametrial recurrence were incidental (7%), but for GTV<sub>CRX</sub> larger than 130 cm<sup>3</sup> (gr. D) local recurrence rate increased to 13% and in the left parametrium to 20%.

Periaortal lymph nodes metastases (PAM) occurred during follow-up (fig. 2) were the major cause of failure (24%). They occurred mainly when the GTV<sub>CRX</sub> was larger than 44 cm<sup>3</sup> and significantly ( $p < 0.001$ ) more frequent ( $\geq 40\%$ ), if the EQED<sub>2.0</sub> to the right parametrium were lower than 54 izeGy<sub>2.0</sub> (tab. III). The PAM never developed when the left parametrium received EQED<sub>2.0</sub> of  $\geq 60$  izeGy<sub>2.0</sub>.

### EQED<sub>2.0</sub> dose – risk of periaortal nodes metastases

Present results show that an underdosed right parametrium has likely been the main source of cancer cells that spread to the periaortal lymph nodes, although the incidence of three cervical local failures (group C and D) should not be ignored. Accumulated incidence of (PAM) as a function of follow-up time is shown in figure 2.



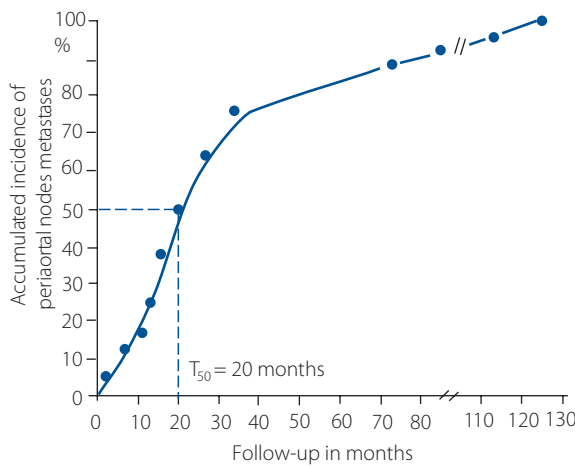
**Figure 1.** Topographical graph of cervix (GTV<sub>CRX</sub>) and parametria (GTV<sub>LP</sub>, GTV<sub>RP</sub>) volumes contoured and counted on serial CTS

**Table I.** Characteristics of cervical (GTV<sub>CRX</sub>) and parametrial (GTV<sub>LP</sub>, GTV<sub>RP</sub>) subgroups

Subgroup	No. cases		GTV <sub>CRX</sub> cm <sup>3</sup>	GTV <sub>LP</sub> cm <sup>3</sup>	GTV <sub>RP</sub> cm <sup>3</sup>
A	13	10%	5–7	2–3	2–3
B	93	69%	25–35	2.2–4.2	2.2–4.1
C	14	10%	44–75	3.5–4.4	3.0–4.4
D	15	11%	130–300	4.0–4.6	4.0–4.7

**Table II.** A – local tumour control (LTC) of the cervix and parametria depending on volumetric status (A–D) and EQED<sub>2.0</sub> doses; B – incidence of the PAM developing on parametrial volumes (A–D) and respective EQED<sub>2.0</sub> doses

Total EQED <sub>2.0</sub> (izoGy <sub>2.0</sub> )	5-years local tumour control											
	Cervix				Parametrium							
					Left				Right			
	A	B	C	D	A	B	C	D	A	B	C	D
≤55									100%	100%		
55.1–60					100%	100%	75%	75%	100%	100%	88%	
60.1–67					100%	100%	100%	88%		100%	100%	77%
105–110		100%		33%								
110.1–115	100%	100%	93%	92%								
>115	100%		100%	100%								



**Figure 2.** Accumulated incidence of periaortal nodal metastases occurring during follow-up

**Table III.** Risk of parametrial lymph nodes metastases depending on EQED<sub>2.0</sub> doses and cervical GTV<sub>CRX</sub>

EQED <sub>2.0</sub> in right parametrium	GTV <sub>CRX</sub> volumetric subgroups			
	A	B	C	D
≥51 izoGy <sub>2.0</sub>	50%	62%	100%	100%
51–53		17%	100%	100%
53.1–56	0%		66%	50%
56.1–59	0%	0%	0%	12%
60–64	0%	0%	0%	0%
65–67	0%	0%	0%	0%
	PAM NO RISK			

About 80% of the PAM occurred within 40 months of follow-up. From figure 2, the T<sub>50</sub> parameter (time of evidence of 50% of to be PAM) at 20 months was estimated. Assuming that 10<sup>2</sup>–10<sup>3</sup> cancer cells are enough to develop a nodal metastatic lesion, the T<sub>50</sub> indicated its repopulation kinetics doubling

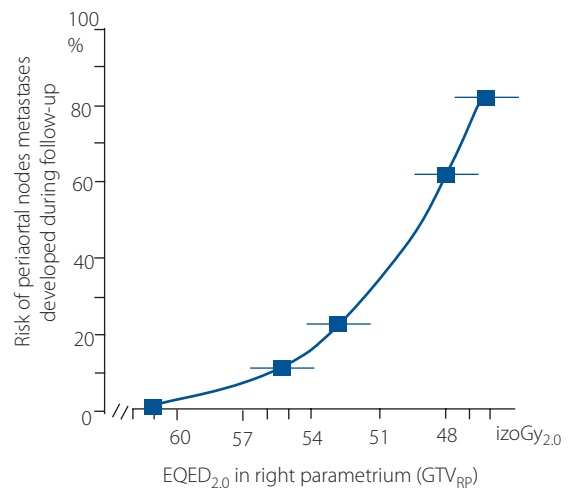
time of about 20–30 days. This may explain that 10–15% PAM occurred late, after 80 months of follow-up.

Figure 3 illustrates the significant increase in the PAM when the EQED<sub>2.0</sub> doses delivered to the right parametrium were lower than 55 izoGy<sub>2.0</sub>. It has to be pointed that the EQED<sub>2.0</sub> doses were estimated in the midline of each parametrium. Therefore, its outer parts were even more underdosed, because of the high dose gradient using the 3D-IMRT technique.

Table III illustrates the significant increase in the risk of PAM (LP, RP) when the midline parametrial EQED<sub>2.0</sub> becomes lower than 53 izoGy<sub>2.0</sub>, especially if the GTV<sub>CRX</sub> volume increases to more than 44 cm<sup>3</sup>.

### EQED<sub>2.0</sub> – GTV<sub>CRX</sub>, GTV<sub>LP</sub> and GTV<sub>RP</sub> control relationship

The incidences of cervix local control (LCC) and parametrial control (LPC) have been counted separately because of pronounced differences in the EQED<sub>2.0</sub> doses delivered to these two targets. Figure 4 shows 100% LCC for GTV<sub>CRX</sub> up to 35–40 cm<sup>3</sup>



**Figure 3.** Risk of periaortal metastases depending on EQED<sub>2.0</sub> doses delivered to the right parametrium (GTV<sub>RP</sub>)

(gr. A and B) for the EQED<sub>2.0</sub> doses higher than 110 izoGy<sub>2.0</sub>. For GTV<sub>CRX</sub> larger than 130 cm<sup>3</sup>, EQED<sub>2.0</sub> lower than 110 Gy<sub>2.0</sub> results in only 50% LCC, which steeply increases to 100% if EQED<sub>2.0</sub> gets higher than 116 izoGy<sub>2.0</sub>.

Local parametrial control (LPC) was 100% for EQED<sub>2.0</sub> higher than 60–65 izoGy<sub>2.0</sub>, independently of their initial volumes, which does not differ very much (2–4.5 cm<sup>3</sup>) within the four analysed subgroups. However, when midline EQED<sub>2.0</sub> was lower than 60 izoGy<sub>2.0</sub> the LPC (group D) sharply decreases below 60% (fig. 4). It is also important that a parametrial EQED<sub>2.0</sub> lower than 55 izoGy<sub>2.0</sub> (usually in the right parametrium) with initial GTV<sub>CRX</sub> higher than 44 cm<sup>3</sup> led to a higher incidence of PNM occurring during follow-up.

On the contrary, too high LCC and LPC, metastases to the periaortal lymph nodes (PNM) were the major failure, which developed in 24% of cases during follow-up. The risk of the PNM increased steeply for parametrial EQED<sub>2.0</sub> doses lower than 54–55 izoGy<sub>2.0</sub>. Such an underdosed parametrium can likely become a potential source of spread of the surviving cancer cells to the periaortal lymph nodes (fig. 3) to develop metastatic lesions. Uncontrolled cervix with GTV<sub>CRX</sub> higher than 130 cm<sup>3</sup> receiving EQED<sub>2.0</sub> <110 izoGy<sub>2.0</sub> should not be ignored, because it may also contribute to increasing the risk of the PNM (tab. III, gr. C and D).

## Discussion

In radiotherapy for locally advanced cervix cancer (IIb and IIIb), delivery of adequate doses to both the primary tumour and the involved parametria is a major determinant of high long-term local control. In the majority of studies, treatment outcome has been usually related to the rank of FIGO stage. Studies on radiotherapy efficacy related to initial cervix (GTV<sub>CRX</sub>) and left and right parametria (GTV<sub>LP</sub>, GTV<sub>RP</sub>) volumes has been incidentally explored, although Dubben et al. [11]

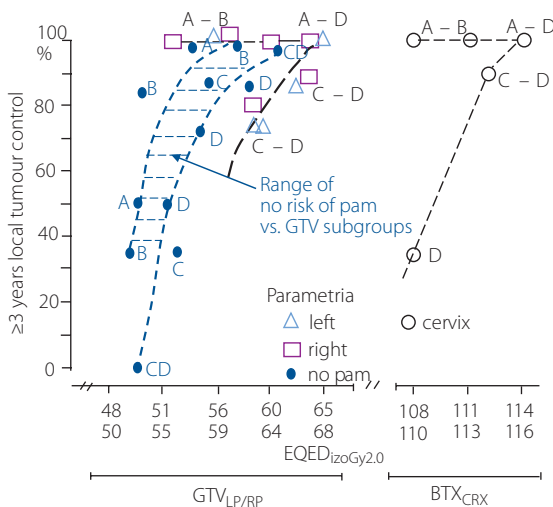
convincingly documented cervix target volume as being the only significant predictor for treatment outcome. In the EMBRACE trial [2], the importance of volumetric staging was quantified in a group of 481 patients with cervix cancer in stage IIb and IIIb. All data was divided into five volumetric subgroups with a mean GTV in the range of 12.6–79.4 cm<sup>3</sup>. Mean total dose (D<sub>100</sub>) was in the range of 88.3–103.1 Gy. However, the “dose-volume-local control relationship” was not accounted for in the analysis, and the authors have only confined themselves to the conclusion that cervical and parametrial volumes in cervix cancers stage IIb and IIIb represent a great degree of heterogeneity and radiation doses should be individually tailored to target volumes.

In the present study, instead of the rank FIGO stages, cervix (GTV<sub>CRX</sub>) and parametria (GTV<sub>LP</sub>, GTV<sub>RP</sub>) volumes were estimated and subdivided into four volumetric groups. Table I shows a wide range of cervix GTV<sub>CRX</sub> within 2 FIGO stages, whereas parametria volumes (GTV<sub>LP</sub> and GTV<sub>RP</sub>) did not differ very much. EXRT and BRT total physical doses were normalised to EQED<sub>2.0</sub> if given in 2.0 Gy fraction, using the L-Q model. A relatively high biological EQED<sub>2.0</sub> delivered to the cervix resulted in a high rate (98%) of 5-year LCC.

Local parametrial control (LPC) was also high, close to 96%. Unexpectedly, EQED<sub>2.0</sub> doses within the right parametrium were about 15–20% lower than within the left one. The large gradient of the HDR dose within a short distance beyond the point A may suggest its relatively small contribution to the total parametrial EQED<sub>2.0</sub>. The 3D-IMRT also characterises heterogeneous dose distribution with a steep decrease outside of the cervix target volume [19, 20], and also in the peripheral part of the parametrium being out of its midline. Therefore, these areas can likely receive EQED<sub>2.0</sub> doses lower than 60 izoGy<sub>2.0</sub> as noted in case of right parametria. However, 5-year local parametrial control has not significantly differed from that noted for the cervix. The FIGO Cancer Report [1] and EMBRACE [2] studies pointed out that parametrial doses should not be lower than 60–65 izoGy<sub>2.0</sub> as noted for the left parametrium in the present study.

On the contrary, too high LCC and LPC, and metastases to periaortal lymph nodes (PAM) during follow-up occurred as a major cause of failure (24%). The risk of the PAM steeply increased when parametrial EQED<sub>2.0</sub> doses became lower than 54–55 izoGy<sub>2.0</sub>. Such underdosage to the parametrium can likely be a potential source of spread of the survived cancer cells to the PNM (fig. 2) to develop metastatic lesions. The impact of uncontrolled GTV<sub>CRX</sub> higher 130 cm<sup>3</sup> (EQED<sub>2.0</sub> <110 izoGy<sub>2.0</sub>) on the risk of the PAM also cannot be ignored (tab. II).

Perez and Karanagh [17], and Girinsky, Rey and Rache [20] indicated overall treatment time (OTT) as one of the major predictors of treatment outcome, also for cervix cancer. However, in the present study OTT did not differ significantly, being in the range of 49–54 days, and therefore impact of time factor on treatment outcome was ignored.



**Figure 4.** Local cervical and parametrial control depending on the EQED<sub>2.0</sub> doses

## Conclusion

The results presented clearly show a wide range of cervix cancer volumes within two FIGO stages (IIB and IIIB), and differences in the delivered biological total doses (EQED<sub>2.0</sub>), mainly between the left and right parametria GTV<sub>(LP,RP)</sub>. This convincingly suggests that the volumetric status of the cervix and parametria, even within the same FIGO ranks, can be a useful measurable predictor for treatment planning which should avoid “dose cold spots” (<55 izoGy<sub>2.0</sub>) in the parametrium. A cervix volume higher than 44 cm<sup>3</sup> with biological total dose lower than 115 izoGy<sub>2.0</sub> and parametrial “dose cold spots” (<55 izoGy<sub>2.0</sub>) may likely result in an increasing risk of development of periaortic lymph node metastases during follow-up. Therefore, such situation needs re-planning of dose distribution within the respective cervix and parametria volumes and prophylactic irradiation of the periaortic region should likely be considered.

**Conflict of interest:** none declared

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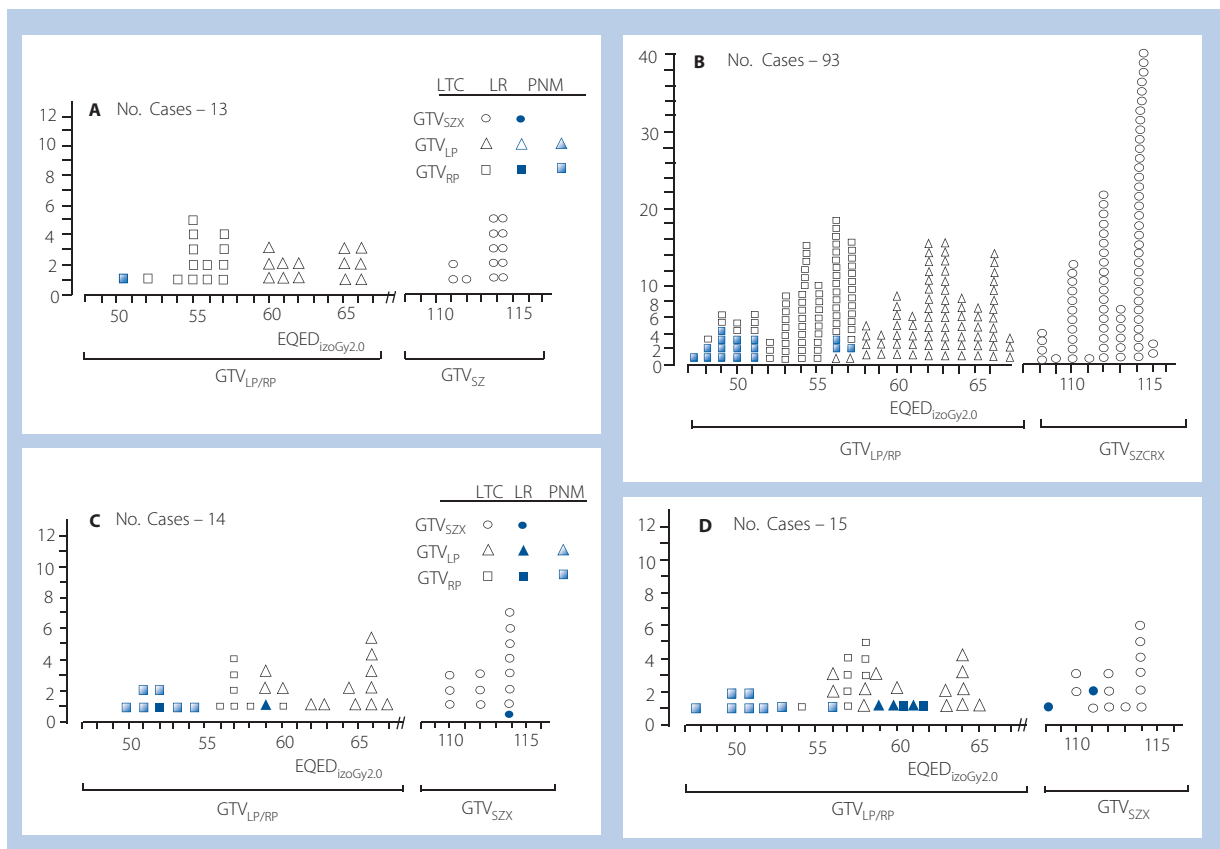
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**Appendix 1.** Histograms of local tumour control of the cervix and parametria cancer lesion and the incidence of periaortic lymph node metastases in the group A, B, C, D (LTC – local tumour control, LR – local recurrence, PAM – periaortic lymph node metastases)

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