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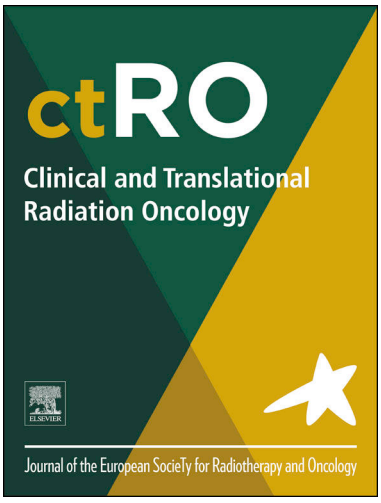

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Predictive clinical and dosimetric parameters for risk of relapse in early-stage non-small cell lung cancer treated by SBRT: a large single institution experience

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Short title : Predictive outcomes in early-stage non-small cell lung cancer

Abstract:

Purpose: To evaluate the impact of dosimetric parameters on efficacy of stereotactic body radiation therapy (SBRT) in early-stage non-small cell lung cancer (ES-NSCLC), using Hypofractionated Treatment Effects in the Clinic (HyTEC) reporting standards.

Methods : From April 2010 to December 2020, 497 patients who received SBRT for ES-NSCLC at the University Hospital of Liège were retrospectively enrolled. A total dose of 40 to 60 Gy in 3-5 fractions (72-180 Gy biologically effective dose with an α/β ratio of 10 (BED_{10})) was prescribed to the 80 % isodose line of the PTV. Potential clinical and dosimetric predictors of recurrence, overall survival (OS) and disease specific survival (DSS) were evaluated using univariate and multivariate analyses.

Results : After a median follow-up of 32 months (range 3-143 months), the local control and disease-free survival (DFS) rates at 3 years were 91% (95% CI: 90 %–93 %) and 75% (95% CI: 73%–77%), respectively. The median OS was 41.6 months and the median DSS was not reached. On multivariate analysis, a higher gross tumor volume (GTV) D_{max} (BED_{10}) (cut-off 198 Gy) and a larger percent of the GTV receiving ≥110% of the prescribed dose were predictive of a better local control, only GTV volume was correlated with DSS and no parameter was correlated with OS and regional or distant recurrences.

Conclusion : Lung SBRT for ES-NSCLC in 3 to 5 fractions resulted in high local control rates. A higher percent of GTV receiving ≥110% of the prescribed dose and a higher GTV D_{max} (BED_{10}) seem to allow a better local control.

Keywords: early-stage non-small cell lung cancer; Stereotactic body radiation therapy; dosimetric analysis; local control; relapse

Introduction

Stereotactic body radiation therapy (SBRT) has become a therapeutic standard for inoperable early-stage non-small cell lung cancer (ES-NSCLC) based on the results of numerous studies that have reported very good local control (LC) and low toxicity rates [1–3]. However, due to its quick development [4–6], SBRT is performed on several different types of machines (linear accelerator or dedicated machine) and prescribing methods vary widely between centers, with dose reports often insufficient to determine the optimal dose prescribing method. Total dose, dose fractionation, dose prescription site and dose distribution inhomogeneity are often reported but a number of dosimetric parameters are missing such as target volume coverage, as highlighted in the recent Hypofractionated Treatment Effects in the Clinic (HyTEC) report [7]. Thus, this review proposed recommendations on the dose report to be provided in order to improve the accuracy of the tumor control probability (TCP) models [7]. These detailed reports should include standard parameters such as the definition of the gross tumor volume (GTV), the method of accounting for respiratory motion, and the margins for planning target volume (PTV) expansion because it has been shown that doses in the GTV can vary by 20-30%, depending on whether the dose is prescribed at the isocenter, to cover a certain percentage of the PTV, or prescribed at a specific isodose line (e.g. 80%). Such differences may distort the interpretation of dose-outcome relationships. Other potentially relevant parameters should be added to the dose ratio such as the percentage of GTV receiving more than 110% of the prescribed dose (PD), the GTV D95% or the percentage of coverage of microscopic extension if a particular technique is used to take it into account. In addition, it is necessary to have all the potentially confounding clinical parameters such as the histology of the treated tumors, the medical operability status of these patients and the location of the tumor to have the most reliable dose-outcome models [7]. Finally, the fractionation used may also be different. In Japan, following a prospective clinical trial of SBRT for stage I NSCLC (JCOG0403) [1], the standard prescription is 48 Gy in four fractions from the isocenter [8], whereas in the United States and Europe, the three-fraction scheme delivering 54 to 60 Gy to the periphery of the PTV is the most commonly used [9–11]. Thus, to compare the different fractions it seems necessary to report the doses delivered in biologically effective dose (BED).

Therefore, the aim of this study was to analyze the efficacy outcomes of lung SBRT for ES-NSCLC using the HyTEC reporting standards of the Working Group on Stereotactic Body Radiotherapy (WGSBRT) [7].

Methods

Patients' selection

All consecutive patients treated with lung SBRT between April 2010 and December 2020 from University Hospital of Liège were retrospectively reviewed. Patients with histologically or clinically diagnosed ES-NSCLC T1 (< 3 cm) and T2 (3–5 cm) who were over 18 years old were included. Exclusion criteria were locally advanced NSCLC, metastatic tumors, a history of lung cancer within the last 5 years, incomplete course of SBRT and a concomitant or adjuvant systemic treatment.

For patients who could not undergo or refused biopsy, the clinical diagnosis of NSCLC was validated by multidisciplinary tumor board, including a clinical lung cancer pulmonologist, radiologist, nuclear medicine physician and radiation oncologist, on the basis of strong imaging suspicion showed a high uptake of ^{18}F-fluorodeoxyglucose on positron emission tomography (^{18}F-FDG PET/CT) and an increase in two consecutive computed tomography (CT) scans acquired 3 months apart. Clinical staging of the

lung cancer was performed according to the 8th Union for International Cancer Control TNM staging system using CT, brain imaging (magnetic resonance imaging (MRI) or CT), and ^{18}F-FDG PET/CT.

Clinicopathologic parameters were collected, including age, WHO performance status (PS), clinical stage (T1 or T2), tumor histology, and peripheral versus central [12](defined by a tumor located within 2 cm of the proximal bronchial tree) tumor location and CT characteristics of the tumor (solid, cavitating, ground-glass or necrotic).

The study was approved by the institutional ethical committees.

Treatment

SBRT was administered using a dedicated machine (Cyberknife®, Accuray). Three different tracking options are available for thoracic tumors. For each patient, the most suitable algorithm has been chosen. The fiducial tracking system allows real time tracking of tumors but requires prior transthoracic insertion of fiducial markers in or near the target. The fiducial-free tracking system such as the Xsight Lung Tracking (XLT) system and Lung Optimized Treatment (LOT) have been used in cases where the tumor silhouette is clearly identified on the two ortogonal panels of the X-ray detector allowing to avoid the implantation of markers. The LOT 1-view mode is used when only the craniocaudal movement of the tumor can be identified from a single direction. The XsightSpine® tracking system had been used if neither of the previous tracking system was feasible. In this case, the tracking is performed on the vertebra [13].

Planning CT images were obtained with a slice thickness of 1 mm. Patients were immobilised using an individual vacuum bag in supine position, with arms along the body. All patients had expiration and moderate inspiration CT scans to estimate the extent of tumor movements related to breathing. In case of direct visualization of the tumor or the fiducials, GTV delineation was performed on expiration CT only. In case of fiducials implantation, CT simulation was delayed for a minimum of 10 days after implantation to minimize uncertainty related to potential marker migration. When using The LOT 1-view mode or the XsightSpine® tracking system, an internal GTV was delineated by combining a GTV on the expiration and moderate inspiration CT scans. The vast majority of patients (n = 430; 87%) had ^{18}F-FDG PET/CT in treatment position using the same individual vacuum bag used at the CT simulation, to optimize target volume definition. Margins of 3-4 mm were then applied around the expiratory GTV or around the expiratory and inspiratory GTVs depending on the tracking system to obtain the clinical target volume (CTV). Then, CTV was corrected manually when overlapping with ribs or mediastinal structures. Finally, the definition of the PTV corresponded to a 2-5 mm extension around the CTV.

Treatment plans were obtained with Multiplan® or Precision® treatment planning systems (TPS) (Accuray Inc. Sunnyvale, USA), using Ray Tracing calculation algorithm. We reported all target dose metrics according to the HyTEC reporting standards [7]. In accordance with these reporting standards, we calculated the percentage of the prescription isodose line by dividing the prescribed dose by the maximum dose. We reported the BED using the formula:

$$BED = D \times (1 + [d / (\alpha/\beta)]) \quad (1)$$

where the variables are as follows: d = dose per fraction, in Gy; D = total dose (number of fractions × dose per fraction), in Gy; and α/β ratio = the property of irradiated tissue (10 for the tumor). Prescription doses at the 80% isodose line of PTV varied between 40 to 60 Gy in 3 to 5 fractions (72-180 Gy BED_{10}) depending on proximity to organs at risk (OAR) and on tumor size. Dose constraints to OARs were applied according to international guidelines [14].

Treatment consisted of typically 100–200 non-coplanar beams using Iris® various aperture collimator or fixed collimators in a range between 10 to 60 mm with a dose rate of 600-800 MU/min.

Endpoints

Local failure was defined using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, in which local treatment failure is specified as at least a 20% increase in the longest diameter relative to the previous smallest longest diameter recorded since (and including) the baseline longest diameter equal to an absolute increase of at least 5 mm, or the presence of any new disease (ie, a new separate lesion) within 1.5 cm of the GTV [15]. If possible, recurrence was confirmed histologically via biopsy. If this was not possible, a ^{18}F-FDG PET/CT was performed to confirm the recurrence with an uptake at least equal to the pre-treatment [16]. Regional failure was defined as an involvement of the mediastinal node and metastatic failure was defined as failure in the same pulmonary lobe (farther than 1.5 cm from the primary tumor), in other lung lobes (ipsi or contralateral lung) or in other organs. These recurrences had to be confirmed histologically or by a multidisciplinary committee on the basis of CT and ^{18}F-FDG PET/CT. In the case of death, the cause of death was reported to be cancer-specific or not. Specific death was considered when the patient presented with cancer relapse at the time of death, except for patients with another identified cause of death. All events were measured from the first day of radiotherapy (RT). OS was calculated from the first day of RT to the date of death from any cause. Patients alive at the time of analysis were censored upon the last follow-up. Follow-up was calculated using a reverse Kaplan–Meier estimation [17].

Statistical Analysis

To describe the general behavior of the data, we used standard descriptive statistics. The prognostic factors analyzed were clinical and dosimetric parameters. The log-rank test or univariate Cox regression was used, respectively, for categorical and numerical data to assess the prognostic role of individual variables on LC, disease-free (DFS), regional failure-free (RFS), metastases-free survival (MFS), cancer-specific survival (CSS) and OS. To determine the threshold values for significant parameters (with a p-value ≤ 0.05), the receiver operating characteristic (ROC) curve was used with the Youden index. The multivariate Cox model was used as a method to estimate the independent association of a variable set with a p-value ≤ 0.05 in univariate analyses with outcomes. Survival curves were calculated from the end of SBRT using the Kaplan-Meier method. All statistical analyses were performed using the R++ platform for statistical programming, version 1.5.03 (rplusplus.com).

Results

Patients

This retrospective study included 497 patients with an ES-NSCLC from University Hospital of Liège treated by SBRT with a median follow-up of 32 months (range 3-143 months). Clinical parameters are presented in Table 1. SBRT was chosen as the treatment modality due to medical inoperability or patient preference in 95% and 5% of cases, respectively. Sex ratio (M/F) was 1,5 and median age was 73 years (IQR, 66–79) at the time of irradiation. Seventy-five per cent of the patients had a WHO performance status of 0-1. A previous primary lung neoplasia was described in 57 (11%) patients, with thoracic surgery in 42 patients and thoracic irradiation in 15 patients. In addition, 5 patients had surgery for benign lung lesions and 8 patients had radiation therapy for breast cancer. Tumors were stage T1 in 86% of the patients. Histology was not available for 92 patients (18%). Eighty-six per cent of tumors were peripherally located.

Treatment and dosimetric parameters

Treatment and dosimetric parameters are presented in Table 1.

Real-time tumor tracking was performed in 46% of treatments (n =227) either using gold fiducial based or direct fluoroscopic methods. The median prescribed dose (BED_{10}) was 180 Gy [IQR, 132, 180]. Dose was delivered to the 80% isodose line [IQR, 80, 80] encompassing the PTV. Median GTV D_{Max} (BED_{10}), D_{Mean} (BED_{10}) and D_{Min} (BED_{10}) were 261.7 Gy [IQR, 187.5, 262.5], 221.0 Gy [IQR, 162.8, 237.7] and 169.3 Gy [IQR, 120.7, 192.3], respectively. Median GTV coverage was 100% [IQR : 98%, 100%].

Local control

Eleven percent (56/497) of patients had a local relapse during the follow-up. The 3-year local control rate was 91% (95% CI: 90 %–93 %).

The results of the univariate Cox regression model are reported in Table 2. The majority of dosimetric parameters were significant. Regarding clinical parameters, treatment duration and stage were significantly associated with LC.

In multivariate analysis, percent of GTV receiving >110% of prescribed dose (%GTV>110% PD) (HR: 0.14; 95 % CI: 0.025–0.83, p = 0.04) and GTV D_{max} (BED_{10}) (HR: 0.96; 95 % CI: 0.94–0.98, p = 0.002) were significantly associated with LC.

Figure 1 shows the LC curves obtained using %GTV>110% PD and GTV D_{max} (BED_{10}). For patients with GTV D_{max} (BED_{10}) ≤198 Gy vs those with GTV D_{max} (BED_{10}) >198 Gy, the 3-year local control was 84% (95 % CI: 80–87) vs 96% (95 % CI: 95–98) $P < 0.0001$. For patients with %GTV>110% PD ≤ 83% vs those with %GTV>110% PD >83%, the 3-year local control was 88% (95 % CI: 85–91) vs 94% (95 % CI: 92–96) $P = 0.0043$.

Disease-free, regional failure-free and metastases-free survival

Thirty-nine percent (195/497), 16% (81/497) and 29% (143/497) of patients had any, regional and metastatic recurrence, respectively, during the follow-up.

The 3-year DFS, RFS and MFS rates were 75% (95% CI: 73%–77%), 90% (95% CI: 88%–91%) and 81% (95 % CI: 79%–83%), respectively.

The results of the univariate Cox regression model are reported in Tables 3-5.

In multivariate analysis, no parameters were significantly associated with these outcomes.

Cancer specific survival and overall survival

Twenty-six percent (128/497), and 65% (323/497) of patients have died due to cancer and any cause, respectively, during the follow-up.

The 3-year CSS and OS rates were 81 % (95 % CI: 78%–83%) and 56% (95% CI: 54%–58%), respectively. The median CSS and OS were not reached and 41.6 months, respectively.

The results of the univariate Cox regression model are reported in Tables A1 and A2. The multivariate analysis did not reveal any significant parameters for CSS. In multivariate analysis, WHO PS (HR: 2.12;

95 % CI: 1.65–2.72, p < 0.0001), and gender (HR: 0.77; 95 % CI: 0.60–0.98, p = 0.03) were significantly associated with OS.

Discussion

In this large retrospective monocentric study looking at lung SBRT efficacy in the setting of ES-NSCLC, we found that a larger percent of the GTV receiving ≥110% of the prescribed dose and a higher GTV D_{max} (BED_{10}) resulted in superior local control. To our knowledge, this is the one of the largest retrospective studies which finds a correlation between dosimetric parameters, including the percent of GTV receiving ≥110% of the prescribed dose, and local control in ES-NSCLC treated with SBRT according to the Hypofractionated Treatment Effects in the Clinic (HyTEC) dose reporting standards.

Determining the optimal dose to achieve excellent LC in the treatment of SBRT for ES-NSCLC is essential. Although several studies have reported their local experience [18], it has been highlighted that the majority of these studies did not provide sufficient dose reporting to determine dose-outcome relationship. Indeed, one of the first studies by Onishi et al. showed that the LC was better with a BED of 100 Gy or more than with a BED of less than 100 Gy [19]. Following this publication, a BED of 100 Gy has often been used as a prescription dose target. However, the sites of dose prescription for SBRT planning vary between institutions and is mainly divided into three categories: central prescription in the PTV, peripheral and median prescriptions. Moreover, two meta-analyses found a lack of dose-outcome relationship between nominal BED and SBRT efficacy, including local control [18, 20].

In our study, the majority of patients had a BED in the periphery of the GTV >100 Gy (482/497, 97%) following the publication of Onishi et al [19]. We found that a GTV D_{max} (BED_{10}) >198Gy significantly improved the LC which is consistent with the literature. Some studies showed that the maximum BEDs of PTV were indices correlated with the LC [21–23] and recent systematic review also showed a significant correlation and found a gradual positive correlation between the central BED and LC, with a 30 Gy increase expected to improve the LC rate by 1%, and a central BED of 150 Gy resulted in an LC of 90% [18]. This probably is because the central BED reflects the true gross tumor volume dose and because the peripheral BED does not reflect this dose but only the marginal and lowest doses in the PTV. We also found that a high percent of GTV receiving ≥110% of the prescribed dose improved local control. This is a dosimetric parameter that we analyzed following the recommendations of the HyTEC reporting standards [7]. We did not find any other study that had analyzed this parameter. However, this result supports the hypothesis that it is a high dose in the target that seems essential to obtain a better local control than the dose in the microscopic extension of the disease [7].

The present study confirmed the survival and disease control benefits of SBRT. The 3-year OS and CSS rates were 56% and 81%, which is consistent with previous studies on the use of SBRT in ES-NSCLC [10, 24]. The 3-year CSS and DFS rates in the present study were also close to those of patients treated with surgery [25]. In multivariate analysis, we found that good general condition and female gender were correlated with better overall survival as in previous studies [26]. However, no parameter was independently significant for CSS or DFS.

Some studies have found a dose-outcome relationship for RFS and MFS [22, 27]. However, in our study, many parameters were significant in univariate analysis but no clinical or dosimetric parameter was correlated with the risk of relapse in multivariate analysis as previous studies [28, 29]. These results suggest the need to find predictive biomarkers of relapse risk, such as radiomics or genomics [30, 31] because ongoing studies are evaluating the benefit of concomitant treatment, including immunotherapy, to SBRT (NCT03924869, NCT03050554, NCT03833154). Thus, it would be interesting to have non-invasive tools to select patients at high risk of relapse who could benefit from concomitant or adjuvant systemic therapy.

This study has some limitations. First, this was a retrospective analysis, complete clinical parameters (tobacco, histology) and toxicity were not available for all patients. Moreover, the reason why some patients did not receive a higher dose is not available. It could be the proximity of an organ at risk or in case of new course of RT. Nevertheless, although a higher dose has an impact on LC, the percentage of GTV receiving more than 110% of the prescribed dose is also an independent factor for better LC. This dosimetric parameter could be interesting to increase the probability of LC in patients where a high dose is not feasible. Second, the dose calculation used in this analysis was done with the Ray-Tracing algorithm which does not take into account the inhomogeneity corrections. This leads to a potential overestimation of the delivered dose of 10 to 15% compared to an algorithm type C such as Monte Carlo (MC) which takes into account the inhomogeneity corrections [18, 32]. Since the middle of the analysed period, patient dosimetries were frequently performed both with Raytracing and with MC. We are well aware of the importance of the MC based represcription, based on our in house developed aid for represcription [33]. For patients treated during this historical series however, the prescription used was still the Raytracing plan. To avoid repeat (retrospective) dose calculations, and to maintain methodological homogeneity, this analysis was thus based on the Raytracing plans. However, we can estimate that the optimal MC GTV Dmax (BED10) would be between 153 and 167 Gy by applying the BED formula. LC was assessed using CT and PET-CT based imaging and applying the RECIST version 1.1 and only 45% (25/56) of LF had pathological confirmation. Thus, as SBRT can cause scarring or inflammatory changes making radiographic interpretations difficult, there is some uncertainty in the reported LC rates [16, 34]. Nevertheless, each case was evaluated in a multidisciplinary committee to minimize this bias.

In the current study, we attempted to demonstrate a dose-outcome relationship in ES-SCLC treated with SBRT. Because this was a single-institution study, treatment methods were uniform in many ways, including respiration at planning and treatment, definition of target volumes, dose prescription policy to maximize dose within the target, and accurate target positioning. Therefore, this study could potentially resolve many errors that can occur in aggregated studies. Although a monocentric study also represents limitations, as it is generally considered that results can only be generalized to centers using the same treatment protocol. We should note that the parameters significantly predictive of local control underline the importance of dose prescription heterogeneity irrespective of the dose prescribed, which can be applied whatever the type of accelerator or dose calculation algorithm used. The GTV D_{max} (BED_{10}) had already been reported in previous studies. However, the percentage of the GTV receiving ≥110% of the prescribed dose had never been reported in the literature. This parameter is significantly predictive of local control independently of the prescribed dose or GTV D_{max} (BED_{10}), which could guide SBRT planning if the prescribed dose or D_{max} cannot be increased due to proximity to an organ at risk.

Conclusion

Lung SBRT for ES-NSCLC in 3 to 5 fractions resulted in high local control rates. A higher percent of GTV receiving ≥110% of the prescribed dose and a higher GTV D_{max} (BED_{10}) seem to allow a better local control.

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Tables

Table 1. Clinical and treatment parameters

	Overall (N=497)
Age	
Median [Q1, Q3]	73 [66, 79]
Gender	
Male	298 (60%)
Female	199 (40%)
Performance status	

	Overall (N=497)
0-1	373 (75%)
2-3	124 (25%)
Weight	
Median [Q1, Q3]	69 [57, 82]
Body mass index	
Median [Q1, Q3]	25 [21, 29]
Tobacco	
Yes	448 (90%)
No	25 (5%)
Unkown	24 (5%)
Previous thoracic radiation therapy	
No	474 (95%)
Yes	23 (5%)
Previous thoracic surgery	

	Overall (N=497)
No	450 (91%)
Yes	47 (9%)
Histology	
Adenocarcinoma	209 (42%)
Squamous cell carcinoma	173 (35%)
Unknown	92 (18%)
Others (Large cell carcinoma and not otherwise specified)	23 (5%)
Tumor stage	
T1	425 (86%)
T2	72 (14%)
Localization	
Peripheral	427 (86%)
Central	70 (14%)
Imaging appearance	

	Overall (N=497)
Solid	441 (89%)
Cavitation	31 (6%)
Ground-glass	15 (3%)
Necrosis	10 (2%)
Tracking method	
Xsight spine	270 (54%)
Synchrony	151 (31%)
Xsight Lung	76 (15%)
Delay between PET/CT and treatment in days	
Median [Q1, Q3]	16 [9, 39]
Prescribed dose (BED_{10}) in Gy	
Median [Q1, Q3]	180 [132, 180]
Number of fraction	

	Overall (N=497)
Median [Q1, Q3]	3 [3, 5]
Dose by fraction in Gy	
Median [Q1, Q3]	20 [12, 20]
Treatment duration in days	
Median [Q1, Q3]	6 [5, 9]
Prescription isodose line	
Median [Q1, Q3]	80% [80, 80]
GTV volume in cc	
Median [Q1, Q3]	5.94 [2.95, 12.19]
CTV volume in cc	
Median [Q1, Q3]	13.43 [7.57, 23.88]
PTV volume in cc	
Median [Q1, Q3]	19.99 [12.01, 33.5]

	Overall (N=497)
GTV D_{Max} (BED_{10}) in Gy	
Median [Q1, Q3]	261.66 [187.5, 262.5]
GTV D_{Mean} (BED_{10}) in Gy	
Median [Q1, Q3]	221.03 [162.76, 237.72]
GTV D_{Min} (BED_{10}) in Gy	
Median [Q1, Q3]	169.26 [120.74, 192.3]
GTV $D_{95\%}$ (BED_{10}) in Gy	
Median [Q1, Q3]	187.01 [138.46, 212.55]
GTV coverage	
Median [Q1, Q3]	100% [98%, 100%]
Percentage of GTV >110% of prescribed dose	
Median [Q1, Q3]	89% [74%, 98%]
D_{Max} CTV (BED_{10}) in Gy	

	Overall (N=497)
Median [Q1, Q3]	262.5 [187.5, 262.5]
D_{Mean} CTV (BED_{10}) in Gy	
Median [Q1, Q3]	218.99 [160.15, 229.44]
D_{Min} CTV (BED_{10}) in Gy	
Median [Q1, Q3]	153.37 [108.4, 177.01]
CTV coverage	
Median [Q1, Q3]	100% [97, 100]
PTV D_{Max} (BED_{10}) in Gy	
Median [Q1, Q3]	262.5 [187.5, 262.5]
PTV D_{Mean} (BED_{10}) in Gy	
Median [Q1, Q3]	211.79 [154.32, 220.26]
PTV D_{Min} (BED_{10}) in Gy	
Median [Q1, Q3]	129.89 [90.75, 159.02]

	Overall (N=497)
PTV coverage	
Median [Q1, Q3]	97% [92, 99]

Abbreviations : BED_{10}= biologically effective dose with an α/β ratio of 10 ; GTV=Gross tumor volume ; CTV=Clinical target volume ; PTV=Planning target volume

Table 2 : Univariate and multivariate analysis for local control (LC).

Subgroup	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*p-value*	HR	95 % CI	*p-value*
Age	1.01	[0.99, 1.02]	0.10	-	-	-
Gender (Male vs Female)	0.84	[0.49, 1.43]	0.51	-	-	-
PS (0-1 vs 2-3)	1.36	[0.73, 2.54]	0.34	-	-	-
BMI	1.03	[0.98, 1.08]	0.27	-	-	-
Weight	1.00	[0.99, 1.02]	0.82	-	-	-
Tobacco (Yes vs no)	1.56	[0.66, 3.67]	0.23	-	-	-
Previous radiation therapy (No vs yes)	0.62	[0.15, 2.54]	0.47	-	-	-
Previous surgery	0.65	[0.24, 1.80]	0.38	-	-	-

Histology			0.68	-	-	-
• Adenocarcinoma (ref)				-	-	-
• Squamous cell carcinoma	1.38	[0.77, 2.48]		-	-	-
• Others	0.97	[0.29, 3.24]		-	-	-
• Unknown	0.98	[0.43, 2.21]		-	-	-
Stage (T1 vs T2)	2.01	[1.31, 3.1]	**0.003**	1.07	[0.58, 1.99]	0.82
Localization (Peripheral vs central)	2.06	[0.91, 4.68]	0.12	-	-	-
Imaging appearance						
• Solid (ref)			0.72	-	-	-
• Cavitation	1.03	[0.37, 2.85]		-	-	-
• Ground-glass	0.40	[0.055, 2.88]		-	-	-
• Necrosis	1.58	[0.22, 11.50]		-	-	-
Treatment duration	1.16	[1.07, 1.26]	**0.0004**	1.04	[0.88, 1.23]	0.65
Delay PET/CT	1.00	[1.00, 1.00]	0.24	-	-	-
Dose prescribed	0.94	[0.89, 0.98]	**0.012**	0.98	[0.81, 1.35]	0.63

Dose prescribed (BED)	0.98	[0.98, 0.99]	**<0.0001**	0.94	[0.76, 1.17]	0.57
Number of fractions	1.78	[1.36, 2.33]	**<0.0001**	6.25	[0.0046, 85.38]	0.61
Dose by fraction	0.87	[0.82, 0.93]	**<0.0001**	2.03	[0.094, 43.52]	0.65
Motion management			0.12			
• Xsight Spine (ref) • Synchrony • Xsight lung	0.91 2.34	[0.49, 1.68] [1.16, 4.71]				
GTV volume	1.02	[1.01, 1.03]	**0.001**	1.01	[0.98, 1.04]	0.18
CTV volume	1.02	[1.01, 1.02]	**0.0005**	1.01	[0.99, 1.02]	0.24
PTV volume	1.01	[1.01, 1.02]	**0.0005**	1.01	[0.99, 1.02]	0.25
GTV D_{Max} (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	0.96	[0.94, 0.98]	**0.0017**
GTV D_{Mean} (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	1.04	[0.99, 1.10]	0.14
GTV D_{Min} (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	0.99	[0.98, 1.01]	0.44
GTV $D_{95\%}$ (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	1.01	[0.97, 1.04]	0.64

GTV coverage	0.044	[0.0079, 0.24]	**0.0016**	0.038	[0.0037, 3.95]	0.36
Percentage of GTV >110% of prescribed dose	0.24	[0.066, 0.86]	**0.037**	0.14	[0.025, 0.83]	**0.043**
D_{Max} CTV (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	1.00	[0.97, 1.05]	0.80
D_{Mean} CTV (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	0.99	[0.95, 1.02]	0.42
D_{Min} CTV (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	1.00	[0.99, 1.01]	0.53
CTV coverage	0.15	[0.027, 0.81]	**0.006**	0.037	[0.0043, 3.18]	0.35
PTV D_{Max} (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	1.00	[0.96, 1.04]	0.95
PTV D_{Mean} (BED_{10})	0.99	[0.98, 0.99]	**<0.0001**	1.00	[0.96, 1.05]	0.85
PTV D_{Min} (BED_{10})	0.99	[0.98, 0.99]	**0.0002**	1.00	[0.99, 1.01]	0.86
PTV coverage	0.055	[0.0022, 0.14]	**0.005**	0.025	[0.0056, 10.83]	0.23
Prescription isodose line	4.06	[2.18, 7.55]	**0.005**	0.52	[0.050, 5.44]	0.34

Abbreviations : PS : Perfomans status ; BMI=Body mass index ; BED_{10}= biologically effective dose with an α/β ratio of 10 ; GTV=Gross tumor volume ; CTV=Clinical target volume ; PTV=Planning target volume

Table 3 : Univariate and multivariate analysis for disease free survival.

Subgroup	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*p-value*	HR	95 % CI	*p-value*
Age	1.00	[0.98, 1.01]	0.52	-	-	-
Gender (Male vs Female)	0.92	[0.69, 1.23]	0.58	-	-	-
PS (0-1 vs 2-3)	1.45	[1.04, 2.02]	**0.036**	1.36	[0.96, 1.93]	0.094
BMI	1.00	[0.97, 1.03]	0.92	-	-	-
Weight	1.00	[0.99, 1.01]	0.49	-	-	-
Tobacco (Yes vs no)	0.76	[0.40, 1.45]	0.22	-	-	-
Previous radiation therapy (No vs yes)	1.15	[0.65, 2.03]	0.63	-	-	-
Previous surgery	1.24	[0.81, 1.89]	0.33	-	-	-

Histology			0.24	-	-	-
• Adenocarcinoma (ref)				-	-	-
• SCC	0.88	[0.64, 1.22]		-	-	-
• Others	1.28	[0.75, 2.18]		-	-	-
• Unknown	0.70	[0.44, 1.10]		-	-	-
Stage (T1 vs T2)	2.01	[1.31, 3.09]	**0.0034**	1.22	[0.85, 1.75]	0.30
Localization (Peripheral vs central)	1.62	[0.80, 3.47]	0.25	-	-	-
Imaging appearance						
• Solid (ref)			0.45			-
• Cavitation	0.80	[0.43, 2.47]		-	-	
• Ground-glass	0.22	[0.055, 1.90]		-	-	
• Necrosis	2.84	[1.25, 6.41]		-	-	
Treatment duration	1.08	[1.03, 1.13]	**0.0018**	1.04	[0.96, 1.14]	0.37
Delay PET/CT	1.00	[1.00, 1.00]	0.72	-	-	-
Dose prescribed	0.96	[0.93, 0.99]	**0.0076**	0.99	[0.94, 1.21]	0.59

Dose prescribed (BED)	0.99	[0.98, 0.99]	**<0.0001**	0.96	[0.84, 1.09]	0.50
Number of fractions	1.31	[1.13, 1.52]	**0.0005**	2.00	[0.035, 11.08]	0.74
Dose by fraction	0.93	[0.90, 0.97]	**0.0001**	1.50	[0.25, 8.94]	0.65
Motion management			0.15			
• Xsight Spine (ref) • Synchrony • Xsight Lung	0.92 2.25	[0.66, 1.27] [0.94, 3.29]				
GTV volume	1.01	[1.01, 1.02]	**0.0006**	1.01	[0.99, 1.02]	0.32
CTV volume	1.01	[1.00, 1.02]	**0.0010**	1.00	[0.99, 1.01]	0.35
PTV volume	1.01	[1.00, 1.01]	**0.0009**	1.00	[0.99, 1.01]	0.69
GTV D_{Max} (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	0.99	[0.97, 1.01]	0.48
GTV D_{Mean} (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	1.01	[0.99, 1.03]	0.27
GTV D_{Min} (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	1.00	[0.99, 1.01]	0.74
GTV $D_{95\%}$ (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	1.01	[0.99, 1.04]	0.19

GTV coverage	0.0030	[0.00024, 0.038]	**<0.0001**	0.094	[0.0020, 4.50]	0.47
Percentage of GTV >110% of prescribed dose	0.47	[0.23, 0.98]	**0.05**	1.02	[0.21, 5.02]	0.98
D_{Max} CTV (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	1.00	[0.97, 1.02]	0.77
D_{Mean} CTV (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	1.00	[0.98, 1.02]	0.82
D_{Min} CTV (BED_{10})	0.99	[0.99, 0.99]	**0.00022**	1.00	[0.99, 1.01]	0.31
CTV coverage	0.0044	[0.00044, 0.043]	**<0.0001**	0.015	[0.0025, 8.41]	0.18
PTV D_{Max} (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	1.00	[0.98, 1.03]	0.90
PTV D_{Mean} (BED_{10})	0.99	[0.99, 0.99]	**<0.0001**	1.00	[0.97, 1.02]	0.82
PTV D_{Min} (BED_{10})	0.99	[0.99, 0.99]	**0.0011**	1.01	[1.00, 1.01]	0.074
PTV coverage	0.015	[0.0024, 0.089]	**<0.0001**	0.025	[0.0036, 1.77]	0.088
Prescription isodose line	2.01	[0.50, 8.08]	0.10	-	-	-

Abbreviations : PS : Perfomans status ; BMI=Body mass index ; BED_{10}= biologically effective dose with an α/β ratio of 10 ; GTV=Gross tumor volume ; CTV=Clinical target volume ; PTV=Planning target volume

Table 4 : Univariate and multivariate analysis for regional failure-free survival

Subgroup	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*p-value*	HR	95 % CI	*p-value*
Age	0.99	[0.97, 1.02]	0.59	-	-	-
Gender (Male vs Female)	0.85	[0.54, 1.34]	0.49	-	-	-
PS (0-1 vs 2-3)	1.33	[0.78, 2.26]	0.30	-	-	-
BMI	1.00	[0.99, 1.01]	0.92	-	-	-
Weight	1.00	[0.96, 1.05]	0.90	-	-	-
Tobacco (Yes vs no)	0.75	[0.27, 2.08]	0.21	-	-	-
Previous radiation therapy (No vs yes)	1.35	[0.59, 3.11]	0.50	-	-	-
Previous surgery	1.31	[0.69, 2.48]	0.42	-	-	-
Histology			0.24	-	-	-
• Adenocarcinoma (ref)				-	-	-
• SCC	0.97	[0.59, 1.59]		-	-	-
• Others		[0.29, 2.31]				
• Unknown	0.82			-	-	-

	0.87	[0.45, 1.68]		-	-	-
Stage (T1 vs T2)	1.43	[0.95, 2.15]	0.10	-	-	-
Localization (Peripheral vs central)	1.88	[0.95, 3.72]	0.21	-	-	-
Imaging appearance						
• Solid (ref)			0.44			-
• Cavitation	0.87	[0.35, 2.16]		-	-	
• Ground-glass	0.92	[0.55, 2.87]		-	-	
• Necrosis	4.46	[1.62, 12.28]		-	-	
Treatment duration	1.06	[0.98, 1.14]	0.15	-	-	-
Delay PET/CT	1.00	[0.99, 1.00]	0.15	-	-	-
Dose prescribed	0.94	[0.90, 0.98]	**0.0039**	0.98	[0.94, 1.12]	0.44
Dose prescribed (BED)	0.99	[0.98, 1.00]	**0.0029**	0.97	[0.92, 1.03]	0.37
Number of fractions	1.26	[0.99, 1.59]	0.059	-	-	-
Dose by fraction	0.93	[0.88, 0.98]	**0.011**	1.07	[0.88, 1.31]	0.49

Motion Management			0.10			
• Xsight Spine (ref) • Synchrony • Xsight Lung	1.24 2.23	[0.76, 2.02] [0.91, 4.16]				
GTV volume	1.02	[1.01, 1.03]	**0.0021**	1.00	[0.98, 1.02]	0.99
CTV volume	1.01	[1.01, 1.02]	**0.0047**	1.00	[0.99, 1.02]	0.52
PTV volume	1.01	[1.00, 1.02]	**0.0056**	1.00	[0.99, 1.01]	0.47
GTV D_{Max} (BED_{10})	0.99	[0.98, 0.99]	**0.0028**	0.99	[0.96, 1.02]	0.54
GTV D_{Mean} (BED_{10})	0.99	[0.98, 0.99]	**0.0040**	1.01	[0.95, 1.07]	0.75
GTV D_{Min} (BED_{10})	0.99	[0.98, 0.99]	**0.020**	1.01	[0.99, 1.02]	0.48
GTV $D_{95\%}$ (BED_{10})	0.99	[0.98, 0.99]	**0.0078**	1.00	[0.97, 1.04]	0.85
GTV coverage	0.085	[0.0050, 14.57]	0.38	-	-	-
Percentage of GTV >110% of prescribed dose	0.55	[0.17, 1.75]	0.32	-	-	-
D_{Max} CTV (BED_{10})	0.99	[0.98, 0.99]	**0.0034**	0.99	[0.96, 1.04]	0.98

D_{Mean} CTV (BED_{10})	0.99	[0.98, 0.99]	**0.0030**	0.99	[0.97, 1.03]	0.90
D_{Min} CTV (BED_{10})	0.99	[0.98, 0.99]	**0.030**	1.00	[0.99, 1.01]	0.64
CTV coverage	0.057	[0.0077, 4.25]	0.22	-	-	-
PTV D_{Max} (BED_{10})	0.99	[0.98, 0.99]	**0.0033**	0.99	[0.96, 1.03]	0.79
PTV D_{Mean} (BED_{10})	0.99	[0.98, 0.99]	**0.0034**	1.00	[0.96, 1.05]	0.86
PTV D_{Min} (BED_{10})	1.00	[0.99, 1.00]	0.13	-	-	-
PTV coverage	0.20	[0.071, 5.82]	0.37	-	-	-
Prescription isodose line	25.01	[0.011, 58.39]	0.54	-	-	-

Abbreviations : PS : Perfomans status ; BMI=Body mass index ; BED_{10}= biologically effective dose with an α/β ratio of 10 ; GTV=Gross tumor volume ; CTV=Clinical target volume ; PTV=Planning target volume

Table 5 : Univariate and multivariate analysis for metastases-free survival

Subgroup	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*p-value*	HR	95 % CI	*p-value*
Age	0.99	[0.98, 1.01]	0.57	-	-	-
Gender (Male vs Female)	0.92	[0.66, 1.29]	0.63	-	-	-
PS (0-1 vs 2-3)	1.39	[0.94, 2.06]	0.11	-	-	-
BMI	0.99	[0.96, 1.03]	0.73	-	-	-
Weight	0.99	[0.99, 1.01]	0.48	-	-	-
Tobacco (Yes vs no)	0.62	[0.27, 1.40]	0.34	-	-	-
Previous radiation therapy (No vs yes)	1.46	[0.80, 2.65]	0.24	-	-	-
Previous surgery	1.45	[0.91, 2.31]	0.13	-	-	-

Histology			0.23	-	-	-
• Adenocarcinoma (ref)				-	-	-
• SCC	0.77	[0.53, 1.12]		-	-	-
• Others	1.01			-	-	-
• Unknown	0.62	[0.52, 1.96]		-	-	-
		[0.37, 1.06]				
Stage (T1 vs T2)	1.59	[1.19, 2.14]	**0.0036**	1.43	[0.98, 2.06]	0.068
Localization (Peripheral vs central)	1.29	[0.72, 2.32]	0.42	-	-	-
Imaging appearance						
• Solid (ref)			0.13			-
• Cavitation	0.69	[0.32, 1.47]		-	-	
• Ground-glass	0.15			-	-	
• Necrosis	2.51	[0.021, 1.08]		-	-	
		[0.92, 6.80]				
Treatment duration	1.07	[1.02, 1.13]	**0.015**	1.04	[0.95, 1.15]	0.40
Delay PET/CT	1	[0.99, 1.01]	0.89	-	-	-
Dose prescribed	0.97	[0.94, 1.01]	0.17	-	-	-

Dose prescribed (BED)	0.99	[0.99, 1.00]	**0.0087**	0.99	[0.85, 1.14]	0.87
Number of fractions	1.26	[1.06, 1.50]	**0.0093**	1.98	[0.018, 24.93]	0.78
Dose by fraction	0.95	[0.91, 0.98]	**0.0065**	1.41	[0.17, 11.49]	0.75
Motion management			0.34			-
• Xsight Spine (ref) • Synchrony • Xsight lung	0.88 2.37	[0.59, 1.29] [1.53, 3.66]		- -	- -	
GTV volume	1.01	[0.99, 1.02]	0.076	-	-	-
CTV volume	1.01	[0.99, 1.01]	0.12	-	-	-
PTV volume	1.01	[0.99, 1.01]	0.11	-	-	-
GTV D_{Max} (BED_{10})	0.99	[0.99, 1.00]	**0.0031**	0.99	[0.97, 1.01]	0.32
GTV D_{Mean} (BED_{10})	0.99	[0.99, 1.00]	**0.0044**	0.99	[0.96, 1.02]	0.40
GTV D_{Min} (BED_{10})	0.99	[0.99, 0.99]	**0.0056**	0.99	[0.98, 1.01]	0.67
GTV $D_{95\%}$ (BED_{10})	0.99	[0.99, 0.99]	**0.0051**	1.02	[0.99, 1.04]	0.15

GTV coverage	0.37	[0.019, 0.72]	**0.0014**	0.17	[0.057, 2.61]	0.13
Percentage of GTV >110% of prescribed dose	0.51	[0.22, 1.22]	0.14	-	-	-
D_{Max} CTV (BED_{10})	0.99	[0.99, 0.99]	**0.0065**	1.00	[0.98, 1.03]	0.82
D_{Mean} CTV (BED_{10})	0.99	[0.99, 0.99]	**0.0024**	0.99	[0.97, 1.02]	0.60
D_{Min} CTV (BED_{10})	0.99	[0.99, 0.99]	**0.018**	1.01	[0.99, 1.02]	0.13
CTV coverage	0.52	[0.035, 0.76]	**0.00074**	0.42	[0.076, 4.47]	0.25
PTV D_{Max} (BED_{10})	0.99	[0.99, 0.99]	**0.0079**	1.01	[0.98, 1.04]	0.51
PTV D_{Mean} (BED_{10})	0.99	[0.98, 0.99]	**0.0016**	0.99	[0.96, 1.02]	0.42
PTV D_{Min} (BED_{10})	0.99	[0.99, 0.99]	**0.046**	1.01	[1.00, 1.01]	0.11
PTV coverage	0.14	[0.017, 0.87]	**0.00024**	0.13	[0.027, 6.17]	0.15
Prescription isodose line	5.26	[0.67, 41.55]	0.090	-	-	-

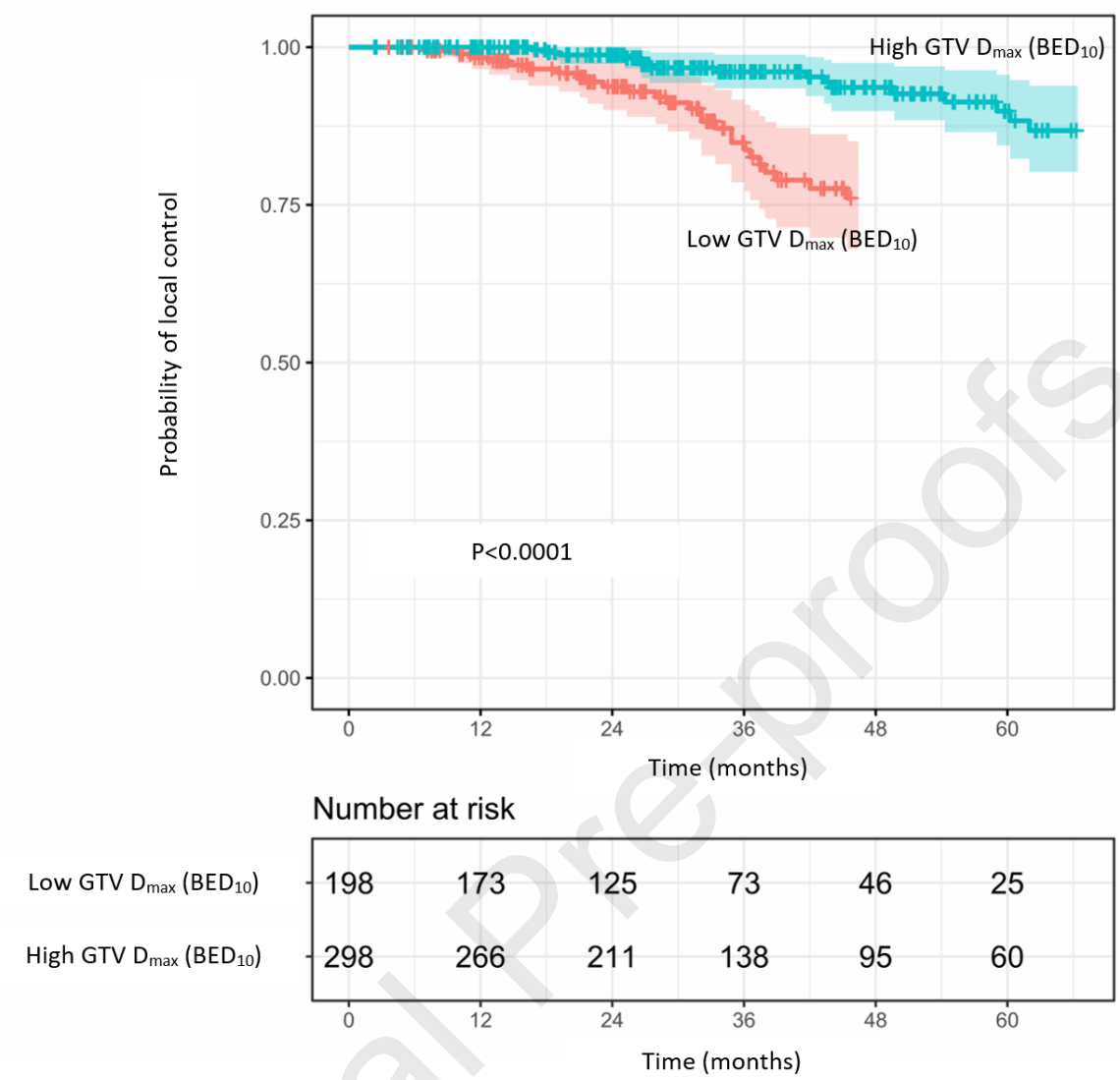
Abbreviations : PS : Perfomans status ; BMI=Body mass index ; BED_{10}= biologically effective dose with an α/β ratio of 10 ; GTV=Gross tumor volume ; CTV=Clinical target volume ; PTV=Planning target volume

Highlights :

- Impact of dosimetric parameters on efficacy of SBRT in ES-NSCLC, using Hypofractionated Treatment Effects in the Clinic reporting standards.
- A large cohort from a single institution to ensure consistent treatment methods .
- This study could potentially resolve many errors that can occur in pooled studies.
- A higher percent of GTV receiving ≥110% of the prescribed dose and a higher GTV D_{max} (BED_{10}) seem to allow a better local control.
- This is the first study to report the benefit of the percentage of GTV receiving ≥110% of the prescribed dose on local control

FIGURE 1. Probability of local control according to GTV D_{max} (BED_{10}) (A) and percent of GTV receiving >110% of prescribed dose (%GTV>110% PD) (B).

A.



B.