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A priori quality assurance using a benchmark case of the randomized phase 2 GORTEC 2014-14 in oligometastatic head and neck cancer patients [= Assurance qualité a priori par un cas de référence de l'essai randomisé de phase II du GORTEC 2014-14 OMET de patients en situation oligométastatique de cancers épidermoïdes ORL]

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A priori quality assurance using a benchmark case of the randomized phase 2 GORTEC 2014-14 in oligometastatic head and neck cancer patients.

Running title: Benchmark case of randomized phase II GORTEC 2014-04

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Abstract:

Purpose: A BC was performed as part of the quality assurance process of the randomized phase 2 GORTEC 2014-14 OMET study, testing the possibility of multisite stereotactic radiation therapy (SBRT) alone in oligometastatic head and neck squamous cell carcinoma (HNSCC).

Material and methods: Compliance by the investigating centers with the prescription, delineation, planning and evaluation recommendations available in the research protocol were assessed. In addition, classical dosimetric analysis was supplemented by quantitative geometric analysis using conformation indices.

Results: Twenty centers participated in the BC analysis. Among them, four major's deviations (MaD) were reported in two BCs. Two (10%) centers in MaD had omitted the satellite tumor nodule and secondarily validated their contouring after fix. Their respective DICE indexes were 0.37 and 0. These two centers were also in material major unacceptable deviation. One (5%) center was finally excluded from the study.

Conclusion: A priori QA using a BC conditioning the participation of the clinical investigation centers showed deviations from good SBRT practice and led to the exclusion of one out of the twenty participating centers. The majority of centers have demonstrated rigorous compliance with the research protocol. The uses of quality index add a complementary approach and guaranty an additional level of quality.

Key words: cancer, head and neck, stereotactic radiotherapy, clinical trial, quality assurance, deviation, benchmark case

Disclosures: none

Titre

Assurance qualité a priori par un Benchmark Case de l'essai randomisé de phase II GORTEC 2014-14 OMET de patients en situation oligométastatique de cancers épidermoïdes ORL.

Résumé

Objectif

Un cas de référence a été réalisé dans le cadre du processus d'assurance qualité de l'étude randomisée de phase 2 du **roupe d'Oncologie Radiothérapie Tête Et Cou** (GORTEC) 2014-14 OMET, testant la possibilité d'une radiothérapie stéréotaxique multisite (SBRT) exclusive pour des cancers épidermoïdes oligométastatiques de la sphèreORL.

Matériel et méthodes

Le respect par les centres investigateurs des recommandations de prescription, de délinéation, de planification et de dosimétrie définis par le protocole de recherche a été évalué, par l'intermédiaire d'un cas clinique test conditionnant leur participation à l'étude. De plus, l'analyse dosimétrique classique a été complétée par une analyse géométrique quantitative utilisant des indices de conformation.

Résultats

Vingt centres investigateurs ont participé au test. Quatre déviations majeures ont été signalées pour deux cas test. Deux (10%) centres investigateurs en déviation majeure ont omis un nodule tumoral satellite et ont validé secondairement leurs contours après correction. Leurs indices de DICE respectifs étaient à 0,37 et à 0. Ces deux centres étaient également en déviation majeure matérielle. Un (5%) centre investigateur a finalement été exclu de l'étude.

Conclusion

Cette étude cas test conditionnant la participation des centres investigateurs a mis en évidence des écarts par rapport aux bonnes pratiques de la radiothérapie stéréotaxique et a conduit à l'exclusion d'un centre parmi les vingt participant. La majorité des centres ont démontré un respect rigoureux du protocole de recherche et ont obtenu des résultats satisfaisants quant à leur pratique. L'utilisation des indices de qualité dosimétriques a apporté approche complémentaire et a garanti un niveau de qualité supplémentaire.

Mots clés : cancer, ORL, radiothérapie stéréotaxique, essai clinique, assurance qualité, déviation, benchmark case.

Title

A priori quality assurance using a benchmark case of the randomized phase 2 GORTEC 2014-14 in oligometastatic head and neck cancer patients.

Abstract

Introduction

A Benchmark Case (BC) study was performed as part of the quality assurance process of the randomized phase 2 GORTEC 2014-14 OMET study, testing the possibility of multisite stereotactic radiation therapy (SBRT) alone in oligometastatic head and neck squamous cell carcinoma (HNSCC).

Material and methods

Compliance by the investigating centers with the prescription, delineation, planning and evaluation recommendations available in the research protocol were assessed. In addition, classical dosimetric analysis was supplemented by quantitative geometric analysis using conformation indices.

Results

Twenty centers participated in the BC analysis. Among them, four major's deviations (MaD) were reported in two BCs. Two (10%) centers in MaD had omitted the satellite tumor nodule and secondarily validated their contouring after fix. Their respective DICE indexes were 0.37 and 0. These two centers were also in material major unacceptable deviation. One (5%) center was finally excluded from the study.

Conclusion

A priori QA using a BC conditioning the participation of the clinical investigation centers showed deviations from good SBRT practice and led to the exclusion of one out of the twenty participating centers. The majority of centers have demonstrated rigorous compliance with the research protocol. The uses of quality index add a complementary approach and guaranty an additional level of quality.

Key words: cancer, head and neck, stereotactic radiotherapy, clinical trial, quality assurance, deviation, benchmark case

Introduction

Metastatic cancer is an advanced state of cancerous disease with various stages ranging from a unique metastasis to wide-spread dissemination. This metastatic disease heterogeneity is associated with different prognoses. The concept of oligometastases¹ was proposed to define a stage of limited metastatic distribution with an intermediate^{2,3} prognosis in which prolonged systemic tumor control may be obtained. To do so, treatments may rely on local ablative multisite stereotactic body radiation therapy (SBRT) rather than systemic treatment alone⁴. On one hand, the indirect so-called abscopal effect produced with the irradiation of some metastatic targets seems anecdotal in head and neck cancers. On the other hand, targeted multisite treatment in consolidation with systemic treatment⁵ or as an exclusive treatment⁶ has been shown to provide a benefit in overall survival in several types of cancer.

The current standard of care for metastatic HNSCC consists in systemic therapy with palliative intention^{7,8,9}. However, tolerance is limited and side-effects of systemic treatment may deteriorate quality of life. The numbers of efficient and tolerable systemic treatment lines are limited in usually heavily pretreated patients in their locally advanced stage. Recently introduced into the therapeutic arsenal, immunotherapy seems beneficial, but only in a subset of patients and its action can be delayed for several weeks. The COMET trial included too few patients with HNSCC¹⁰ in order to evaluate the benefit of an exclusive ablative treatment by SBRT^{6,11}. Furthermore, locoregional progression is associated with a substantial risk of death, a notable difference compared to other disease sites of the COMET trial. The treatment of oligometastatic HNSCC¹² patients with SBRT could present a survival advantage while preserving quality of life. This treatment could also help postpone the initiation of systemic therapy thus delaying potential side effects and further preserving quality of life.

The GORTEC 2014-04 OMET study is a randomized phase 2 study evaluating platinum-based chemotherapy combined with SBRT compared to exclusive SBRT for oligometastatic HNSCC for intra or extra cranial targets.

When a randomized clinical trial uses a new or insufficiently mastered radiotherapy technique, any deviation from the radiotherapy protocol can significantly compromise the dose distribution in the target volumes and affect tissue response, survival or toxicity of this treatment¹³. At the study's inception in 2014 in France, SBRT, in its extracranial sites, was a

relatively effective and mature technology having a TRL (Technology readiness level) of 8, but clinical investigator experience was heterogeneous with less than 5 years of practice for some centers. We therefore made the participation of the clinical investigation centers conditional on the prior validation of a quality assurance process using a unique anonymized clinical case communicated by the sponsor to each of the centers independently (benchmark case, BC). The main goal of this study was to review these BC submissions in order to guarantee a priori a sufficient level of quality of SBRT to confidently interpret the subsequent results obtained in the trial. The BC results are presented here.

Materials and methods:

***A priori* radiotherapy quality assurance (RTQA) by benchmark case analysis**

For this trial evaluating intra- and extracranial SBRT, the international commission of radiation units (ICRU) Level 2 was chosen for the dose distribution reporting. This level corresponds, in GORTEC's adaptive quality control approach, to a IB level (=any phase II or III study testing a new RT technique solely or with a combination of drugs) for the GORTEC 2014-04 trial. According to GORTEC's approach, the level, frequency and verification modalities (data management and monitoring) of the treatment data depend on the level of technological maturity and the main objective of the trial. Level IB requires, in terms of RTQA, a BC test to be sent to each center before patient accrual. A retrospective control of at least 50% of the dose distribution of patients actually treated in the trial in level IB and an independent IDMC analysis were also planned in the protocol after the twentieth patient included in the trial but are not the focus of the current study.

The RTQA expert group set up by the sponsor was blind to the identity of the center at the time of evaluation. Compliance by the investigative centers with the protocol recommendations for delineating target volumes and organs at risk, as well as with the planning and dosimetry recommendations, were assessed by the RTQA expert group and conclusions were sent to the investigating centers.

The BC presented a patient suffering from a T4N1M0 pharyngeal squamous cell carcinoma treated by chemoradiation with cisplatin 100 mg/m² D1-22-43 (cumulative dose 300 mg/m²). Five years later, a 15 mm parahilar pulmonary nodule of the left upper lobe was

discovered on a chest CT-scan, located 2 cm from the mediastinal structures, associated with a 10 mm satellite nodular lesion. Both nodules had increased in size on 2 scans 3 months apart. A PET-scan confirmed these two pulmonary nodules with a maximum SUV of 11.4 with no other metastatic localization and a controlled primary cancer.

The equipment of the participating centers

Twenty French healthcare facilities agreed to participate in the GORTEC 2014-04 trial. The SBRT equipment, breathing monitoring method, and planning system (TPS) software were left to the investigator's choice. Gating or tracking and computational type C algorithm were encouraged due to small fields, moving tumors, heterogenous tissues, but were not made mandatory. Data on equipments, and image guidance / respiratory management were collected.

Delineation

The volumes of interest (GTV, CTV, and their margins for the PTV determination) were defined based on CT and PET/CT. The delineation recommendations were based on those determined by the RTOG and SIRIADÉ atlases. At least the bronchial stem, lungs, esophagus and heart had to be delineated. The bronchial tubes had to be contoured from the carina to the first segmental bronchi. The lungs were contoured individually and in their entirety. The esophagus was delineated from 10 cm above to 10 cm below the PTV. A PRV (planning organ at risk volume) was optional, but three dimensional margin of 2mm was recommended. The heart had to be completely delineated with the pericardium. HDVs (histogram dose volume) were communicated for all volumes of interest and absorbed dose distributions were visualized three-dimensionally (dose matrix in DICOM-RT).

Prescription

Doses and fractions were compared in terms of BED (biological effective doses). The fractionation protocol recommendation was dependent on the proximity of organs at risk and tumor diameter. In order to harmonize SBRT practice across centers, it was recommended to use 3 fractions of 15 Gy for tumors smaller than 3 cm and/or peripheral lung tumors or 5 fractions of 10 Gy if the tumor is larger than 3 cm and/or for central tumors (central tumor defined as located within 2 cm, or in contact, of the proximal bronchial tree

or a tumor immediately adjacent to the mediastina and pericardial pleura). The protocol included a precautionary message urging that there should be no risk of severe toxicity taken in this metastatic disease condition.

Dose distribution evaluation

The BC plan was designed from the averaged of 4D planning scanner transmitted in DICOM-RT format according to the protocol recommendations. The dose to serial organs such as spinal cord, trachea and bronchial stem was evaluated by determining the maximum punctual dose (Dmax). The so-called parallel organs (lungs, heart), were evaluated by the average dose, and the organ volumes receiving X Gy (V_x (%)). A plan was considered satisfactory if the qualitative assessment of the DVH and isodose curves indicated good coverage of the target volume with no excess dose to the organs at risk (OARs). Because DVH and qualitative slice-by-slice analyses, used in the protocol to define deviations, may be insufficient given the complexity of SBRT, quantitative geometric indicators of compliance, coverage and homogeneity were also assessed. These indices were computed using the Artiview software (Aquilab®) to determine the degree of similarity between isodoses, and determine intersections between the tumor contours and those of the healthy tissues by geometric methods. These indices may be useful to compare several treatment plans and to increase the local control rate and reduce complications.

Protocol deviations

Deviations were classified as major or minor as indicated in the protocol sent to the clinical investigation center candidates (Table 1). In the event of divergence from the protocol, a commented report about deviations was sent to the investigation center. A "major deviation" was defined as deflection that potentially affects the disease control or severe treatment-induced toxicity. An investigation center with a major deviation had to resubmit its revised dosimetry until it was in compliance with the recommendations. This also initiated an *a priori* control of the first two patients included. A minor deviation did not require the investigating center to resubmit the BC, but alerted it to a variation that required adaptation.

Analysis by geometric indices

The different indexes are described in the table 2. The conformity index ^{14,15} quantifies the conformity of the dose distribution with the shape and size of the target volume. It corresponds to a ratio of two volumes according to the RTOG formula (equation 1). The conformity degree was also assessed by the Sørensen - Dice ¹⁴ (DSC) coefficient (equation 2), which assesses the similarity of two samples. The closer to 1, the more similar the two samples are.

The coverage Index ^{16, 17} or CO Index (equation3) reflects the coverage of the target volume by the prescribed dose. For our protocol, a minor deviation corresponded to a coverage between 70 and 95%, a major deviation to a value lower than 70%. Coverage was also evaluated with the target coverage index or TCO index ¹⁸ (equation 4) the optimum is 1.

The homogeneity index ^{14, 19} (HI) measures the homogeneous distribution of the dose in the target volume. It corresponds to the equation 5. The dose homogeneity characterizes the uniformity within the target volume of the dose distribution. The optimum ¹⁹ is 1. The RTOG considers as protocol compliant an index < 2 , a value between 2 and 2.5 as a minor deviation, a major deviation if the value > 2.5 . Our protocol did not propose any deviation concerning this parameter.

The OAR Coverage index or OCO index (equation 6) corresponds to the percentage of the volume of an OAR receiving unwanted irradiation. The optimum is 0. We calculated it for the lung tissue which was the only tissue covered by the reference isodose.

The integral dose (ID) ^{14,17} (equation 7) corresponds to the energy received by the patient in joules. This dose must be As Low As Reasonably Achievable according to the ALARA principle. This index provides overall information on the dose received, while also looking at the dose outside the target volume.

The BC plan was uploaded in DICOM-RT format (images, RT Image, RT Structure Set, RT Plan, RT Dose) to the GORTEC RTQA platform. Declarative information (IGRT modalities, equipment) not contained in the DICOM-RT were transmitted via an .doc file. This trial was previously approved by ethics committee.

Statistics

All analyses were descriptive. Qualitative data were summarized using the number, frequency, and quantitative data were summarized by dispersion parameters describing the scattering of individual data around the mean. All analyses were performed using the free R[®] software version 4.0.3.

Results

In 2016, when all clinical test cases were received, investigation centers had been performing intracranial SBRT for 81 months on average (median 60 months; standard deviation 95 months). These centers had carried out their first extracranial SBRT on average 47 months prior to the BC study (median 39 months; standard deviation 31 months).

Five different types of equipment were used. Linear accelerators dedicated to SBRT such as CyberKnife[®] (n=7; 35%) and linear accelerators such as Truebeam[®] (n=8; 40%), Elekta Axesse[®] (n=3; 15%) or Vero[®] (n=1; 5%) were used (Table 2). Center 20, which carried out the clinical case with an HDA[®] Tomotherapy device, could not participate in the study because of a major deviation that could not be corrected. The corresponding TPS were Multiplan[®] (n=7; 35%), Eclipse[®] (n=5; 25%), IplanRTdose[®] (n=3; 15%), Pinnacle[®] (n=2; 10%), Volo[®] (n=1; 5%), Raystation[®] (n=1; 5%) or Xio[®] (n=1; 5%)(table 2).

In 55% (n=11) of the participating centers, respiratory monitoring method was based on gating, 35% (n=7) of the centers used a tracking method and 10% (n=2) did not use a respiratory monitoring method (including center 5, which used 4D scanner, and center 20). Center 20 compensated for the lack of respiratory management by increasing CTV-PTV margins over the tolerances indicated in the protocol. All centers used online IGRT: 70% of the centers 3D IGRT and 30% 2D IGRT.

Two centers (center 5 and center 20) had omitted the satellite tumor nodule and validated their contouring after an initial major deviation. The DICOM-RT structures of the participating centers showed compliance with the OAR's contouring requirements. The recommendations of CTV and PTV margins were applied. The largest cumulative average PTV

diameter was 40.55 mm with a standard deviation of 9.75 mm and an unresolved major deviation for center 20.

A majority of centers (70%) prescribed 50 Gy in 5 fractions considering the tumor location (2cm from the mediastinum) for a BED ($\alpha/\beta=10$) of 75 Gy (table 4) and an average protraction of 10 days. The other centers opted for doses ranging from 50 to 60 Gy in 3 fractions, for BEDs ($\alpha/\beta=10$) ranging from 112 to 180 Gy and an average protraction of 3 to 8 days. Interfraction times were less than 5 days for all centers. Although these prescriptions are relatively heterogeneous, the protocol recommendations were respected. These data are summarized in table 4.

The TPS and dose calculation algorithms (Table 3) were heterogeneous: 40% of the centers used a type A calculation algorithm, 40% a type B algorithm, and only 20% used a type C algorithm. For the same equipment, different types of algorithms could be used in each center, especially for the Cyberknife® for which only one of the six teams used the Multiplan Monte Carlo algorithm.

The dosimetric data were derived from qualitative analysis of HDVs for this lung location (Table 4), and met the OAR's constraints indicated by the protocol.

Figure 1 shows the values of the quality indices (TCO, CI, HI, DICE and CO). Centre 20 had a Dice index of 0 and a TCO index of 0. Centre 1 had a Dice index of 0.6. The other indexes were within the tolerances. The values circled in dashed lines represent the suboptimal values, while the values circled in solid lines correspond to centers values, which were major material deviations to the protocol compliance.

Excluding centers 5 and 20, the mean volumetric DICE index of the PTV was 0.86 (standard deviation 0.08; IQR (Inter Quartile Interval) 0.07). The average conformity index was 1.22 (standard deviation 0.14; IQR 0.19) with a minimum value of 0.91 and a maximum value of 1.47. The average coverage index was 1 (standard deviation 0.03; IQR 0.03) with a minimum value of 0.96. The average homogeneity index was 1.24 (SD 0.08; IQR 0.08) with a median value of 1.24. The highest value was 1.39. The average target coverage TCO index was 97% (standard deviation 2%, median 97%, Q1 96%). The average OCO coverage index was 0.96

(standard deviation 0.56, minimum 0.06 and maximum 2). The average ID was 29,8 joules (standard deviation 6.34, minimum 0.6, maximum 42.9).

Discussion

The quality of radiotherapy in clinical research is an important condition for the interpretation of clinical trials and their extrapolability to standard care^{20,21,22}. The multicenter HeadSTART²³ trial evaluating the addition of tirapazamine (TPZ) to cisplatin (CIS) and radiotherapy for locally advanced HNSCC was negative (two-year OS rates were 65.7% with CIS-RT and 66.2% for the TPZ-CIS-RT association). After taking into account the impact of major deviations from the RT protocol, this trial was secondarily found to be positive. Any major deviation from the radiotherapy protocol can significantly compromise the dose distribution in the target volumes or the OARs and thus influence the response to treatment, survival or toxicity of a treatment. We therefore conditioned the participation of all centers on the prior validation of a quality assurance process using a BC communicated by the promoter to each of the centers independently.

A pragmatic approach was chosen to encourage centers to participate in the trial despite the variability of equipment's, institutional habits, slow accrual and the intense competition with other clinical trials or new available molecules. There was indeed an important material heterogeneity between participating centers going beyond the heterogeneity of equipment manufacturers, using dedicated or polyvalent equipment adapted to SBRT. For the same equipment, versions and options could vary: some CyberKnife® centers had conical collimators; others had a variable multi-leaf collimator either of the IRIS™ type (two superimposed banks of six tungsten segments) or of the InCise MLC® type. In addition, there was also variability due to varying motion management systems, on-board imaging, robotic table or TPS.

This BC allowed us to highlight two major material deviations from the protocol. Center 20 used Tomotherapy equipment without any method for monitoring breathing and thus relevant CTV to PTV margins, which is redhibitory in terms of impact on OARs. Likewise, center 5 did not use any method for monitoring respiration, despite the simulated tumors in this BC being considered mobile. Center 5 secondarily participated in the study with a

respiratory gating method. The other centers complied with the research protocol without any observed deviation after full review. All participating centers reported conducting a daily online IGRT in conformity with the research protocol.

ICRU's 91 report, published in 2018, highlighted the importance of the type of algorithm chosen for dose calculation. The algorithm was not mandatory for this BC due to TPS-specific algorithms and to disagreements between physicists regarding and the use of TPS-based Monte Carlo algorithms for example. Type A algorithms assume that the equilibrium of the secondary particles is maintained and that the energy deposit occurs punctually, at the point of interaction of the incident photon. In this category, there is no modeling of the secondary electron's transport. Category A includes the modified Batho model, Ray tracing and equivalent techniques of tissue air ratio (Pencil beam and equivalent path length). Type A algorithm is limited for the correct simulation of the penumbra of small beams of pulmonary SBRT, as well as the lateral path of electrons. Type A algorithms have a 20-30% accuracy of and are not recommended in the RTOG 0236 trial. Type B algorithms take into consideration non-local energy deposits and electron transport. They include the superposition / convolution method such as the "collapsed cone convolution" (CCC) method and the type Analytic Anisotropic Algorithm (AAA) algorithm, which analytically models the transport of electrons. They allow a correct simulation of the penumbra of the small beams, as well as a lateral and longitudinal consideration of the path of the electrons with 5-10% accuracy. The deterministic methods by Monte Carlo or of the Accuros type allow a complete simulation of the dose deposit, with $\leq 5\%$ accuracy; they are now recommended for SBRT in homogeneous and heterogeneous media. Seventy percent of centers used a type B algorithm in the BC. Agreement is still lacking in France concerning the validity of simplified TPS-based Monte Carlo algorithms, such as used in Multiplan. On the other hand, computation times for full Monte Carlo algorithms are not compatible with routine clinical use. The impact of these algorithms will be evaluated in quality control after the actual treatment of patients in the GORTEC 2014-04 trial.

All centers followed the recommendations regarding delineation of OARs and target volume, except centers 5 and 20, who had omitted one target. This deviation was assessed qualitatively but also quantitatively with DICE index of 0.37 and 0 and TCO values of 0.23 and 0, respectively. In addition to delineation, centers 5 and 20 had inadequate respiration

monitoring and one of the two substantially increased their CTV-PTV margins and therefore target volumes. The use of the DICE index is limited, as concordance increases with increasing target volumes^{18, 24, 25}. We are therefore aware of DICE index limitations: it measures the overlap between volumes (PTV and reference isodose) but it overpenalises small structure and is more permissive with large structure. We therefore used other quality indices to highlight an anomaly not visualized by the DICE index. Excluding centers in major deviation, the CI value of 1.22 (min-max 1.08-1.45) gives greater importance to target coverage than to the quantification of adjacent normal tissues. This index does not take into consideration the form of the prescription isodose. The GORTEC 2014-04 OMET trial RTQA assessment was performed prior to the publication of ICRU91, which proposes Paddick's CI to address this issue. The impact of these quality indices will be sought after the actual treatment of patients in the GORTEC 2014-04 trial. The coverage index indicated good coverage of target volumes. The definition of minor deviation in our protocol was more restrictive than that of the RTOG. Since the recommendations of the RTOG^{24, 26} do not deviate from the protocol, the plans in which the 90% isodose covered the target and the plans in which the 80% isodose covered the target were classified as a minor deviation, while plans in which the 80% isodose line did not fully cover the target were classified as a major deviation. Center 5 had a low DICE index (0.37) as well as a major deviation for the CI (0.06), also had the lowest coverage index at 0.88, in minor deviation from the protocol. In SBRT, because of the large dose gradients used, the prescribed dose can fall off by more than 25% and may result in tumor underdosage or overdosage of the surrounding healthy tissues. The TCO suggested by the ICRU 91, can be used to evaluate the percentage of the target volume covered by the prescription dose. With the exception of two centers with major deviations, all centers had values greater than 95%. None of them presented deviations regarding homogeneity indices.

In the future, the quality metrics integration could provide an additional level of quality control. We recommend the use of 3 indices which are CI, HI and DICE index, which could together assess numerically and tridimensionally: the dose distribution homogeneity as well as target delineation and coverage. We could retain as major deviation (MaD) for DICE index a value less than 0.5; for HI a MaD would be characterized by a value greater²⁴ than 2.5 and as minor deviation (MiD) a value between 2 to 2.5. Regarding the CI index, we recommend

the use of the Paddick's CI¹⁸. One could consider²⁴ as MaD a CI value superior than 2.5 or inferior than 0.9 and as MiD a value between 0.9 to 1.0 or between 2 to 2.5.

After review, excepted center 20 which was excluding, all other centers followed the dose constraints imposed by the protocol. The maximum dose for serial organs. For the heart and lungs, the maximum, mean dose and the volumes receiving 12.5 and 5 Gy respectively. As the study was initiated prior to the ICRU91 publication, the dose ratio has since been modified. It is now recommended to relate the dose to the target without including pulmonary parenchyma (D50% (GTV/CTV)). Recommendations have since been included in the protocol.

This BC of the GORTEC 2014-04 trial identified major deviations from good practice. After revisions and BC resubmission, one of these two centers was able to participate in the study. Despite heterogeneous equipment's, no other major deviation of the prescription, planning or delivery was detected. Further analysis using geometric indices highlighted sub-optimal values not detected with standard criteria. The impact of computation algorithms and quality indexes will be sought in the quality control assessment after the actual treatment of patients in light of the ICRU91²⁷ for SBRT. All true cases will be analyzed retrospectively at the time of trial completion to improve practices and ensure reliable results.

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Figure 1 shows the values of the quality indices (TCO, CI, HI, DICE and CO). Centre 20 had a Dice index of 0 and a TCO index of 0. Centre 1 had a Dice index of 0.6. The other indexes were within the tolerances. The values circled in dashed lines represent the suboptimal values, while the values circled in solid lines correspond to centers values, which were major material deviations to the protocol compliance.

Figure 1: Indexes by center

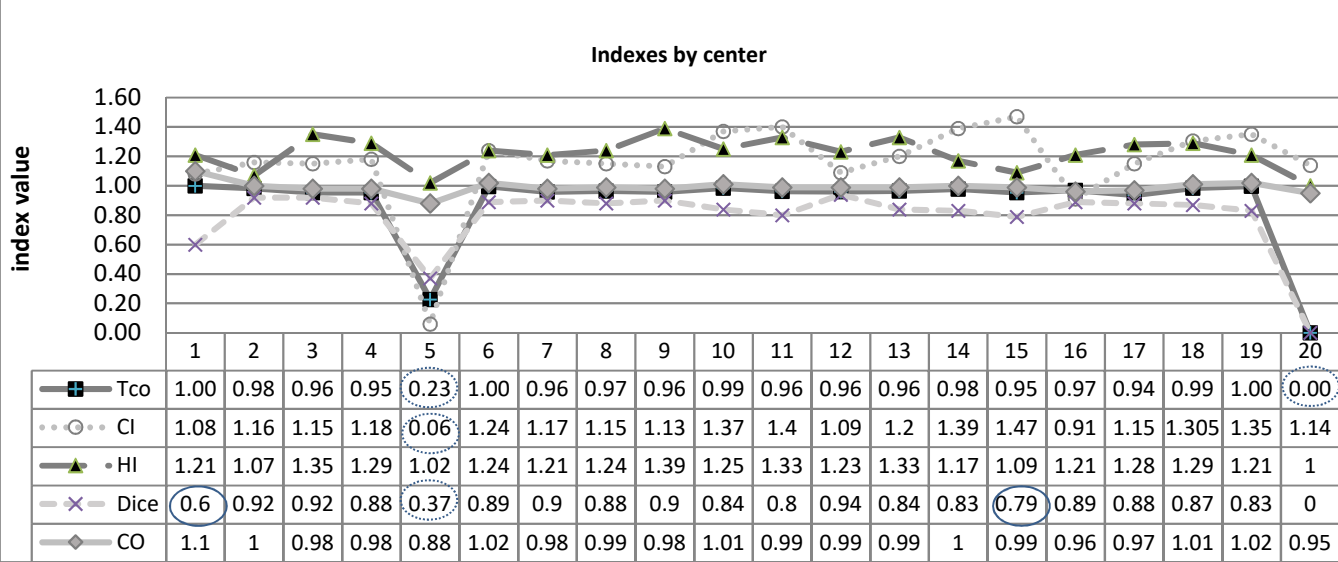


Figure 2 shows the TCO, CI, HI, Dice and CO indices. This representation shows for each of these indices the extreme values, average, and first and third quartile (centers 5 and 20 are excluding).

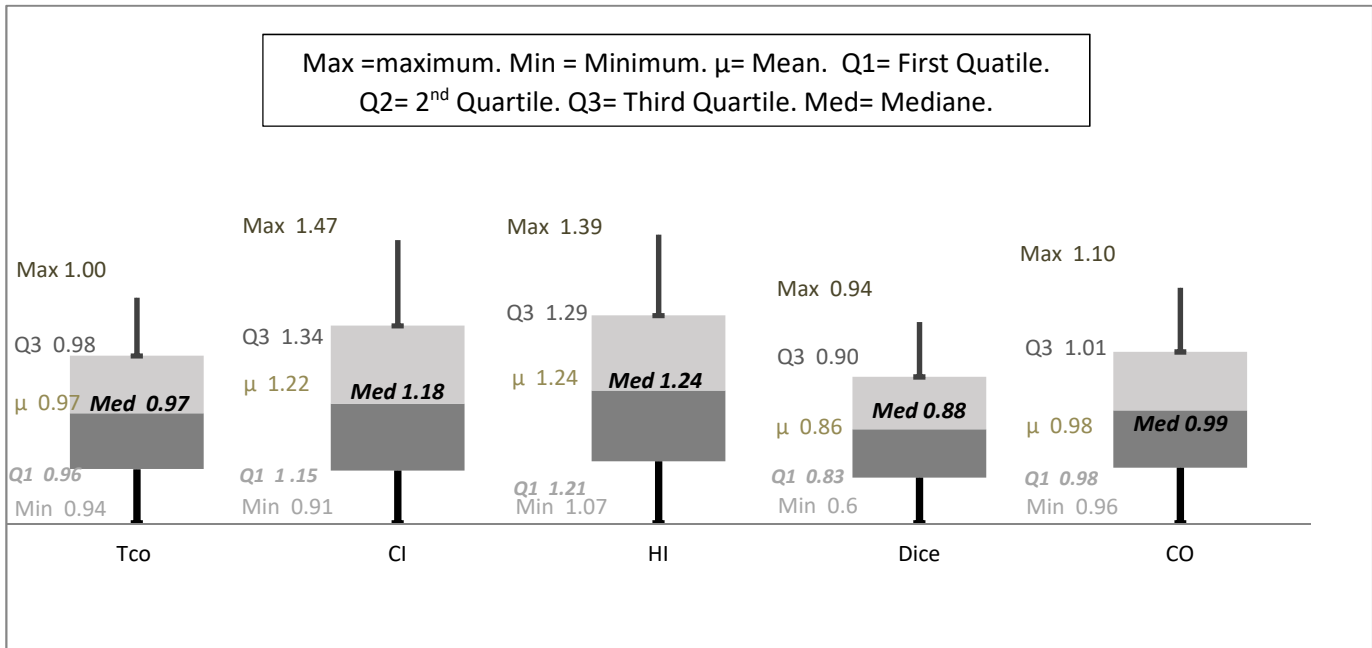


Table 1 : Deviations

Criteria	Major Deviation	Minor Deviation
PTV coverage	≤ 70%	>70 - ≤ 95% (in particular when a critical SRO was attached)
BED	< 50 Gy	< 55 Gy
CTV – GTV Margin	> 10 mm	+ 5-10 mm
PTV – CTV Margin	> 5 mm	
Delineation	≥1 omitted structure (tumor volume or critical OAR)	
Cumulative PTV (all synchronous metastases, sequential or concomitant treatment)	Large diameter > 7 cm	
OARs dose constraints (see table of constraints)	Maximum Dose exceeded for spinal cord, brain stem, optic nerves	Exceeded dose constraints for lungs, liver
Cumulative dose volume histogram for multiple metastases	Missing	Not including all recommended SROs based on metastatic site(s)
Prescription in case of synchronous metastases treated sequentially	Cumulative dose to SROs not taken into account and dose above the threshold on at least one SRO	
Delivered dose	Number of sessions ≤ 2 out of the 3 planned	Number of sessions ≤ 4 out of the 5 planned
Protraction	Interfraction times (for each metastasis) ≥ 8 days	Interfraction times (for each metastasis) ≥ 5 days
Radiotherapy technique	Use of a non-SBRT technique	
IGRT	Not done before each session	Single incidence
Respiratory management	No monitoring mode for mobile tumor with respiration	

All analyzed clinical cases were anonymized both in terms of patient and center identity.

Table 2 : Deviations

Quantification	Index	Abbreviation	Equation	Equation number	Ideal Value
Target volume	Conformity	RTOG CI	$\frac{VR}{VT}$	1	1
		DSC	$2 * \frac{VTR}{VT + VR}$	2	1
	Coverage	CO	$\frac{Dmin}{DR}$	3	1
		TCO	$\frac{VTR}{VT}$	4	1
	Homogeneity	HI	$\frac{Dmax}{DR}$	5	1
Organ at-risk	OCO	OCO	$\frac{VTR}{VT}$	6	0
	Integral Dose	ID	$V * Dmean * Vp$	7	0
Parameter		Description			

Dmax	Point Maximum Dose
Dmin	Point Minimum Dose
DR	Reference Dose = Prescription Dose
VR	Reference Isodose Volume = Prescription isodose Volume
V and VT	Volume and Target Volume
VTR	Volume of the structure (OAR) covered by the reference Dose
Dmean	Mean Dose
Vp	Tissue Density

Table 3: Summary of the main technical characteristics

Centre	Equipment	TPS	Algorithm	If respiratory monitoring method	IG RT	Scan 4D	If 4D scan, breathing monitoring system used
1	Truebeam	Eclipse	AAA	Gating	3D	Yes	GE RT16 / 4D
2	Truebeam	Eclipse	AAA	Gating	3D	Yes	GE Optima RT 580
3	Truebeam	iPlanRTDose 4,5	Convolution/superposition	Gating	2D	Yes	Philips Diaphragmatic Compression
4	Truebeam	Eclipse	AAA	Gating	3D	Yes	RPM
5*	Axesse Elekta (=versa HD)	Pinnacle	Raytracing	None	3D	No	Symmetry Project (CBCT 4D)
6	Truebeam	iplan – Brainlab	Monte Carlo	Gating	3D	Yes	GE Optima RT 580
7	Cyberknife	Multiplan	Ray Tracing	Tracking	2D	Yes	Pneumochest belt bellow, Philips
8	Cyberknife	Multiplan	Ray Tracing	Tracking	2D	Yes	RPM Varian
9	Elekta avec MCL Agility	Xio Elekta	Convolution/Superposition	Gating	3D	Yes	Philips belt 4D
10	VERO	Iplan	Monte Carlo	Gating	3D	Yes	RPM Varian /GE RT16
11	Versa (Elekta)	RayStation (Raysearch)	Collapsed Cone	Gating	3D	Yes	Diaphragmatic compression
12	Cyberknife M6	Multiplan 5.3	Monte Carlo	Tracking	2D	Yes	Philips Brilliance BigBore
13	Cyberknife	Multiplan 5.2.1	Raytracing	Tracking	3D	No	
14	Truebeam	Pinnacle Version 9.10	Raytracing	Gating	2D	Yes	Advantage Sim 4D
15	Cyberknife	Multiplan	Raytracing	Tracking	2D	No	
16	Cyberknife VSI G4	Multiplan v4.6	Raytracing	Tracking	3D	Yes	Philips BigBore
17	Truebeam	Eclipse V11	Acuros	Gating	3D	Yes	RPM (Varian) + scanner GE RT16
18	True beam	Eclipse V11	AAA	Gating	3D	Yes	Gating RPM
19	Cyberknife	Multiplan	Raytracing	Tracking	3D	Yes	Philips BigBore
20*	Tomothérapie HDA	Volo	Convolution Superposition	None	3D	No	

* Centre in major deviation from the protocol application

Table 1: Prescriptions and OAR doses

Prescription Dose (Gy)	Fractions	Centre (Nb)	Centre (%)	BED($\alpha/\beta=10$)	Deviation
45	3	4	20	112.5	None
50	5	13	65	75	None
54	3	1	5	151.20	None
60	3	2	10	180	None

OAR 3 fractions	Constraint	Major deviation	Interval achieved	Average	Deviation
Spinal Cord	Dmax	>22Gy	3.3-8	5.3	None
Main bronchi	Dmax	>30 Gy	6.2-16.4	11.4	None
Trachea	Dmax	>30Gy	0-10	5.3	None
Ribs	Dmax	>37Gy	17-31.1	24.9	None
Heart	Dmax	>30Gy	0.4-3.8	2	None
Heart	V12.5Gy	>24%	0-0	0	None
Heart	V5Gy	>24%	0-0	0	None
Heart	Dmoy	>5Gy	0.1-0.5	0.3	None
Oesophagus	Dmax	>27Gy	4.9-9.6	7.7	None
Esophagus	Dmoy	>27Gy	1.2-11	3.7	None
Homolateral lung	V5Gy	>30%	23.1-48	34.7	None
Homolateral lung	V12.5Gy	>30%	9-26.8	16.4	None
Homolateral lung	Dmoy	>30Gy	5.2-9.8	6.8	None
OAR 5 fractions	Constraint	Major deviation	Interval achieved	Average	Deviation
Spinal Cord	Dmax	>30Gy	2.2-9.9	5.7	None
Main bronchi	Dmax	>38Gy	4.6-36.5	15.5	None
Trachea	Dmax	>38Gy	0.5-15.9	9.2	None
Ribs	Dmax	>43Gy	11.0-30	23	None
Heart	Dmax	>38Gy	0.3-9.9	3.19	None
Heart	V12.5Gy	>32%	0-0	0	None
Heart	V5Gy	>32%	0-4.3	0.5	None
Heart	Dmoy	>5Gy	0-1.3	0.3	None
Esophagus	Dmax	>35Gy	4.9-14.3	8.4	None
Esophagus	Dmoy	>35Gy	0.8-13	3.4	None
Homolateral lung	V5%	>50Gy	21.8-39.4	32.7	None
Homolateral lung	V12.5%	>30 Gy	8.3-25	17.3	None
Homolateral lung	Dmoy	>30Gy	2.4-7.5	5.6	None

The cross-sectional analysis did not provide any evidence of deviation.