Journal of Nuclear Medicine, published on December 9, 2021 as doi:10.2967/jnumed.121.262891

FDG-PET/CT-based prognostic survival model after surgery for head and neck cancer

Gwenaelle Creff (MSc) [1], Franck Jegoux (MD,PhD)[1], Xavier Palard (MD,PhD) [2], Adrien Depeursinge (PhD) [3], Ronan Abgral (MD,PhD)[4], Remi Marianowski (MD,PhD)[5], Jean-Christophe Leclere(MD) [5], Thomas Eugene (MD)[6], Olivier Malard (MD,PhD)[7], Renaud De Crevoisier (MD,PhD)[8,9], Anne Devillers (MD) [2], Joel Castelli (MD,PhD) [8,9].

[1] Department of Otolaryngology–Head and Neck Surgery(HNS), University Hospital, Rennes, France
[2] Department of Nuclear Medicine, Cancer Institute, Rennes, France
[3] Institute of Information Systems, HES-SO, Sierre, Switzerland
[4] Department of Nuclear Medicine, University Hospital, Brest, France
[5] Department of Otolaryngology–HNS, University Hospital, Brest, France
[6] Department of Nuclear Medicine, University Hospital, Nantes, France
[7] Department of Otolaryngology–HNS, University Hospital, Nantes, France
[8] Department of Radiation Oncology, Cancer Institute, Rennes, France
[9]LTSI (Image and Signal Processing Laboratory), INSERM, U1099, 35000, Rennes, France

Corresponding Author :
Ms CREFF Gwenaelle (currently in training (resident))
Department of Otolaryngology–HNS of Rennes University Hospital, F-35000 RENNES, FRANCE
Mail : gwenaelle.Creff@chu-rennes.fr
Tel : 06.87.75.12.95
Fax : 02.99.28.41.94

Short Title : PET prognostic model for HNSCC

Conflict of interest : The authors declare that they have no competing interests.

ABSTRACT

Rationale: The aims of this multicenter study were to identify clinical and preoperative PET/CT parameters predicting Overall Survival (OS) and Distant Metastasis Free Survival(DMFS) from a cohort of Head and Neck Squamous Cell Carcinoma (HNSCC) patients treated with surgery, to generate a prognostic model of OS and DMFS and to validate this prognostic model with an independent cohort.

Materials and Methods: A total of 382 consecutive HNSCC patients divided into training (n=318) and validation cohorts (n=64) were retrospectively included. The following PET/CT parameters were analyzed: clinical parameters, SUVMax, SUVMean, Metabolic Tumor Volume (MTV), Total Lesion Glycolysis (TLG) and distance parameters for the primary tumor and lymph nodes defined by two segmentation methods (relative SUVMax threshold and absolute SUV threshold). Cox analyses were performed for OS and DMFS in the training cohort. The c-index was used to identify highly prognostic parameters. These prognostic parameters were externally tested in the validation cohort.

Results: In multivariable analysis, the significant parameters for OS were T stage and Nodal-MTV, achieving a c-index of 0.64($p<0.001$). For DMFS, the significant parameters were T stage, Nodal-MTV and maximal tumor-node distance (Distance TN), with a c-index of 0.76($p<0.001$). These combinations of parameters were externally validated, achieving c-indices of 0.63($p<0.001$) and 0.71($p<0.001$) for OS and DMFS, respectively.

Conclusion: The Nodal-MTV associated with maximal Distance TN was significantly correlated with the risk of DMFS. Moreover, this parameter in addition to clinical parameters was associated with higher risk of death. These prognostic factors may be used to tailor individualized treatment.

Keywords: Head and neck cancer/ PET-CT/ prognostic/ overall survival/ distant metastasis

INTRODUCTION

The therapeutic management of Head and Neck Squamous Cell Carcinoma (HNSCC) is based on surgery, radiotherapy and medical treatments, alone or in combination, according to the prognosis estimated by the American Joint Committee on Cancer (AJCC) staging system.(*1*)
Despite therapeutic progress and the updating of the AJCC staging system, the prognosis of HNSCC patients remains poor, related to a high recurrence rate of 30-40%.(*2*)

FluoroDeoxyGlucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT) allows us to reveal the metabolic activity of a tumor (glycolysis) in addition to strict anatomic extent. This exam is now commonly used to assess the extent of HNSCC(*3*) and for posttreatment follow-up.(*4*) The effectiveness of FDG-PET/CT parameters as prognostic biomarkers appears to be a promising research path in multiple tumor locations,(*5*–*7*) without additional cost, time, or radiation dose.(*8*). However, fewer data are available for HNSCC patients treated with surgery, although more than half of patients are treated with primary resection. These patients are mostly included in small numbers in the same group of analyses as patients treated with radiochemotherapy, who present with different clinical and histological profiles.

Moreover, while visual analysis is sufficient for diagnosis, staging and the detection of recurrence, quantification appears necessary to predict patient outcome.(*5*) The Maximum Standard Uptake Value (SUVMax) is the most widely used parameter in clinical practice, but it only corresponds to the maximal pixel value in the tumor. More recently, volumetric FDG-PET/CT parameters, i.e., Metabolic Tumor Volume (MTV) and Total Lesion Glycolysis (TLG), which consider overall tumor uptake, have been developed. Moreover, studies on lung cancers introduced the concept of disease solidity(*9*,*10*), which consists of measuring disease spread by computing the relation between the volume of the main tumor and all secondary nodes with respect to the volume of their convex hull(*11*,*12*). This concept has never been analyzed in HNSCC, and volumetric metabolic parameters have never been incorporated into this concept. Nonetheless, computing these parameters requires delineating the tumor. One of the most chosen segmentation methods consists of using a threshold set at 41% of the SUVMax.(*13*) Although there are no consistent data for using this specific threshold to compute MTV,(*14*) Few studies have compared different thresholds of MTV and/or TLG.

Eventually, the lack of FDG-PET/CT acquisition parameter standardization between institutions(*15*) could impact the generalization of the existing data, as most of the studies published so far were monocentric.

In this context, the aims of our study were (1) to identify clinical and preoperative PET/CT parameters predicting Overall Survival (OS) and Distant Metastasis Free Survival (DMFS) from an initial cohort of HNSCC patients treated with surgery, (2) to generate a prognostic model of OS and DMFS, and (3) to validate this prognostic scoring system with a second independent cohort of patients.

MATERIALS AND METHODS

Inclusion Criteria

All consecutive patients from three French hospital centers treated with primary surgery for HNSCC between 1 January 2010 and 31 March 2018 were retrospectively reviewed.

The inclusion criteria are described as follows: 18 years of age or older, no history of cancer, histologically proven HNSCC, preoperative PET/CT, and a minimal follow-up of 3 months.

Carcinoma of unknown primary syndrome, nasopharyngeal, cutaneous and salivary glands squamous cell carcinoma, discovery of distant metastases on the initial extension assessment, SUVMax of primary tumor less than 3 and tumor volume less than 4 mL were systematically excluded from the study.

Access to the oncological network databases was approved by the institutional ethical committees and by the French National Commission for Data Protection and Liberties (CNIL number 2211146) and was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical stan- dards. Confidentiality was assured for all participants regarding any personal responses and information provided, as all data collected were anonymized.

Patient Characteristics And Treatment Results

Of the 3877 patients reviewed, 557 were eligible for the study, and 382 were finally included (Figure1).

All patients underwent tumor resection that could be associated with neck dissection according to the clinical and radiological preoperative stage. Postoperative radiotherapy was performed with or without chemotherapy in patients with a high risk of locoregional recurrence.

Physical examination and laryngoscopy were performed every three months for the first two years, every six months for the next three years and then annually. Database was locked on 31st August 2019.

The entire cohort was divided into a training cohort from Rennes and Brest, including 318 patients, and a validation cohort from Nantes, including 64 patients.

PET/CT Acquisition

All patients underwent FDG-PET/CT for staging before surgical treatment. The PET-CT acquisition parameter data are summarized in the Supplemental-Table 1.

PET/CT Analysis

For each patient, Gross Tumor Volume of the primary Tumor (GTV-T) and of the lymph Nodes (GTV-N) were manually segmented on each PET/CT by the same experienced investigator (radiation oncologist), referring to nuclear radiologist report. This delineation step was performed in axial, coronal and sagittal sections using MIM Software SVVRTMIMS1 (*version* 6.7; *MIM Software Inc*. *Cleveland*, USA, https://www.mimsoftware.com/), with a CT windowing set from -160 to 240 Hounsfield Units and a PET windowing from 0 to 5 SUV. A Region Of Interest (ROI) was then computed by adding a 3D margin of 5 mm to GTV-T (ROI-T) and GTV-N (ROI-N). All lymph nodes were included in the same unique ROI.

A set of quantitative parameters based on SUV histograms were extracted from ROI-T and ROI-N in PET-images using the QuantImage web service(*16*). SUVMax was first computed from ROI-T as the maximum SUV in the delineated volume. Various metabolic volumes were subsequently defined based on two segmentation methods: (i) an absolute threshold of SUV (ranging from 0 to 20, 0.5 by step) or (ii) a relative threshold of SUVMax (from 0 to 100%, 1% by step). Metabolic intensity parameters were computed using the two segmentation methods at each threshold for both ROI-T and ROI-N. Relative thresholds for ROI-N were computed based on SUVMax of the primary tumor. MTV was computed as the metabolic volume of the segmented region in milliliters. If there were several nodes, the MTV-N corresponded to the sum of the MTVs of each node. TLG was computed as SUVMean x MTV of the corresponding delineated region.

Tumor spread, also named disease solidity (*9*), was analyzed by computing various distance measures between the barycenter of the main tumor (ROI-T) and the barycenter of each nodal metastasis (ROI-N) or of all nodal metastases.(*16*)

Statistical Analysis

OS was calculated from the day of the surgery to the date of death from any cause. Patients alive at the time of analysis were censored at the date of last follow-up.

DMFS was calculated from the day of surgery to the date of first distant progression or to the date of death.

Follow-up was calculated using reverse Kaplan-Meier estimation. Both DMFS and OS estimations were computed using the Kaplan-Meier method, and a two-sided log-rank test was used to compare the groups. The analyses were performed as suggested in the TRIPOD statement.(*17*)

In the first step, the analysis was performed only on the training cohort. The association of the pretreatment parameters with OS and DMFS was first assessed using univariable Cox analyses. We used Inverse Probability of Censoring Weighting version of the c-index. Significant parameters were identified ($p<0.05$), and Harrel's c-index was calculated.(*18*) The c-index was used to determine the optimal SUV threshold giving the most predictive value for each PET parameter with a $p<0.1$.

Factors with p-value <0.1 and with the highest c-index after univariable analyses were assessed for the multivariable Cox regression model using backward elimination. Variables were removed from the model if $p>0.1$. Multivariable Cox analyses were performed to identify the significant parameters and the standardized coefficients of the prognostic model.

In the second step, the Cox prognostic models were used to compute the prognostic index for the patients of the validation cohort, and the corresponding c-index of each model was computed.

Based on this model, a nomogram was built to estimate the individual OS and DMFS probability at 24 months.

Two types of validation of the prognostic model were performed. In a first step, an internal validation on the patients from the training cohort was performed by the bootstrap method (1000 datasets constructed by random resampling with replacement from the original). This method was used to estimate the adjusted c-index and the 95% confidence interval (95%CI) of each parameter. In the second step, the ß-coefficients from the training model were applied to the external validation cohort, and the corresponding c-index was computed.

All analyses were performed using R software 3.4.0.

RESULTS

Patient Outcomes

The median OS for the training and validation cohorts was 63months(95%CI=51-not reached) and 91months(95%CI=34-not reached), respectively(p=0.79). For the entire cohort, the 2-year-OS rate was 75%(95%CI=70-80%). In the entire cohort, 35.34% died and 12.83% developed metastasis. Among the patients who died, 36.30% had metastasis. The patient, tumor, treatment and follow-up characteristics of the training and validation cohorts are detailed in Supplemental-Table 2.

Identification Of The Cox Model To Predict OS In The Training Cohort

The results of univariable analysis are given Table 1.

The retained significant parameters from the multivariable analysis were T stage, MTV-N with a threshold of 3 (Figure2). The c-index of the model was 0.64($p<0.001$). The Hazard Ratio(HR) of the corresponding Cox model are presented in Figure2, allowing the calculation of a prognostic index (OS probability) for each patient. Based on the Cox model, a nomogram was computed (Figure3).

Identification Of The Cox Model To Predict DMFS In The Training Cohort

The results of univariable analysis are given Table2.

The retained significant parameters from the multivariable analysis were T stage, MTV-N with a threshold of 3 and maximal tumor-node distance (Figure4). The c-index of the model was 0.76($p<0.001$). The HR of the corresponding Cox model are presented in Figure 4, allowing the calculation of a prognostic index (DMFS probability) for each patient. Based on the Cox model, a nomogram was computed (Figure 5).

Internal And External Validations Of The Prognostic Model

After internal bootstrap validation, the adjusted c-index were estimated at 0.63($p=0.0002$) and 0.74($p<0.001$) for OS and DMFS, respectively. The 95%CIs for the coefficients of the parameters of the model are given in Supplemental-Table3 (OS) and Supplental-Table4 (DMFS). Internal calibration sshowed a good adjustment between the predicted and observed OS and DMFS at 24 months (Supplemental-Figure1/SF2). The ß-coefficients from the training model were applied to the external validation cohort, achieving a c-index of 0.63($p<0.001$) and 0.71($p<0.001$) for OS and DMFS, respectively.

DISCUSSION

To our knowledge, this is the first study presenting an FDG-PET/CT-based prognostic model including the concept of tumor dispersion to stratify the risk of DM and death in patients with HNSCC treated with surgery. In this multicentric study of 382 patients, we demonstrate that the integration of pretreatment PET quantitative imaging features alongside conventional clinical prognostic factors enables the identification of patients with a high risk of distant relapse or death.

Patients with the same stage and type of tumor could respond differently to the same treatment and eventually have different outcomes.(*19*) As we observed in our study, stage cN was not correlated with OS and the AJCC stage had a lower c-index than PET/CT volumetric and distance parameters (Table1 and 2). This result is consistent with reports in the literature among patients with HNSCC treated with radiochemotherapy.(*20*) Indeed, among 470 patients with p16-negative oropharyngeal cancer treated with radiochemotherapy, the c-index of the PET-prognostic model based on SUV-entropy and asphericity was significantly higher than that of clinical parameters (Eastern Cooperative Oncology Group score, O'Sullivan's stage and AJCC stage), achieving a c-index of 0.75 versus 0.57,p<0.001 for ECOG score, 0.58,p<0.001 for O'Sullivan classification and 0.57, p<0.001 for AJCC stage.(*21*)

These new prognostic factors should allow to better identify patients with HNSCC at high risk of recurrence after surgery, with the aim of improving their therapeutic strategy by "personalized medicine",(*22*) based on characteristics inherent to each patient and not on population-based risk assessments such as staging.(*23*)

The first PET parameter to be analyzed was the SUVMax.(*24*) Although easy to use in routine clinical practice, this FDG-PET/CT parameter is now increasingly seen as unreliable as a prognostic factor.(*5*,*14*) Indeed, in our study, the SUVmax was not correlated with OS or DMFS in multivariable analysis. In a cohort of 162 patients with oral cavity carcinoma treated with surgery, pretreatment MTV and TLG were both independent predictive factors for OS (HR=2.64(1.35-5.21),p=0.005 and HR=3.30(1.50-7.24),p=0.003), whereas SUVMax was not (HR=1.92(0.92-3.96),p=0.080).(*25*) In a systematic review of the prognostic value of PET-parameters for patients with surgically treated HNSCC, MTV and/or TLG were found to have a higher prognostic value than SUVMax.(*14*)

Nevertheless, to be used, these volumetric parameters need a specific delineation.(*5*) Four techniques can be used: a threshold of SUV (absolute[all voxels with an SUV value > *x*], relative[>*x*% of SUVmax], or adaptive), gradient-based, clustering, or statistical methods. No consensus has currently been found.(*26*) However, it has been demonstrated that the results vary greatly depending on the segmentation technique used, much greater than the interoperator variability during contouring.(*27*) We chose to use the intensity threshold thanks to its availability in nuclear medicine services, and because our objective was to edit a prognostic model for patients with surgically treated HNSCC usable in routine clinical practice. However, we decided to explore a wide range of continuous thresholds from 0 to 100% SUVMax and from 0 to 20 and not restricting to the usual threshold of 41% of the SUVMax. Indeed the limits of this threshold have already been displayed in patients with HNSCC treated with radiochemotherapy.(*20*,*28*) To our knowledge, there has been no study in the literature that has analyzed different threshold values with such precise segmentation in patients treated with surgery. We demonstrated that MTV of the primary tumor computed with a relative threshold of 23% was significantly associated with OS, with a c-index of 0.64($p<0.001$). This relative threshold is lower than the threshold of 41% currently used. These data are consistent with the threshold that has been demonstrated in patients with locally advanced stage of HNSCC treated with radiotherapy (35% of the SUVMax).(*29*,*30*) Conversely, in cancers of the cervix, among 89 patients treated with radiochemotherapy, a threshold of 50% of SUVMax was most significantly correlated with recurrence-free survival (c-index=0.752, HR=1.065; $p<0.001$).(*31*) Therefore, it appears that the threshold value used for the delineation of the tumor must be adapted to the tumor location and to the prognostic data sought. Indeed, in our study, to predict DMFS and OS, lower thresholds (15-25% of SUVMax) seem more relevant. Despite we performed an external validation, due to the difference with the threshold of 41% used routinely, an additional validation of these thresholds by other groups must be interesting.

In addition to the volume parameters, the tumor dispersion parameters also seemed to be promising, especially for the DMFS (Figure 4). This suggests that the quantitative imaging feature that examines spatial dispersion of the disease may also be relevant for prognosis.(*9*,*32*) Indeed, the parameter of maximum distance between the tumor and the lymph node relay remained correlated with DMFS in multivariable analysis (HR=1.12(1.03;1.21)). For non–small cell lung cancers, the addition of distance parameters to the conventional prognostic factors alone model yielded a significant improvement with the likelihood ratio test ($p=0.007$).(*9*)

Our study had some limitations. First, the analysis was retrospective, which may have an impact regarding the diagnosis of DM. We only included patients with a minimal follow-up of 3 months, to exclude deaths due to surgical complications (not related to oncological evolution). Second, the impact of the heterogeneity of the workflows of acquiring FDG-PET/CT images on the data resulting from the quantification is the subject of debate.(*15*,*26*,*33*) However, we developed a multicenter study with different acquisition parameters and performed an external validation of the prognostic model in an independent population of HNSCC patients. Although the prognostic value of p16 status in oropharyngeal cancer has already been demonstrated(*34*), it was excluded due to a lack of data. Besides, quantitative analyses from 18F-FDG-PET/CT reveal carbohydrate metabolic hyperactivity in tumor cells, named the Warburg effect(*35*). However, some of the cN3 stages and voluminous tumors have a necrotic central part, which is therefore not considered during the extraction of FDG-PET/CT parameters, which underestimates the tumor volume. Other radiotracers could then be used, such as 18F-fluoromisonidazole and 18F-fluoroazomycinarabinoside, which have already demonstrated their potential prognostic interest in terms of OS(*36*) but are not yet used in clinical practice. Conversely, in case of contact between the primary tumor and an involved lymph node, an overestimation of the tumor volume may be calculated due to the inclusion of the lymph node tumor volume in the metabolic volume of the primary tumor. SUVmax less than 3 and tumor volume less than 4mL were excluded to avoid high variability in very small volume. Finally, we exclusively investigated PET/CT imaging; however, PET/MRI image analyses also seem to have an interest in prognostic terms, although they are very rarely performed in HNSCC oncology.(*37*)

CONCLUSION

The volumetric and distance parameters appeared to be independent prognostic factors in terms of OS and DMFS, with higher c-index value than the clinical parameters currently used.

By integrating them into a prognostic model, we could be able to identify HNSCC patients at higher risk of distance relapse and death. These patients could then receive early therapeutic intensification to improve their prognosis.

FINANCIAL DISCLOSURE

The authors declare that they have no competing interests.

KEY POINTS:

Question: The aim of this study was to identify clinical and preoperative PET/CT parameters predicting Overall Survival (OS) and Distant Metastasis Free Survival (DMFS) from a cohort of Head and Neck Squamous Cell Carcinoma patients treated with surgery.

Pertinent findings: In this retrospective multicentric study of 382 patients, the Nodal MTV associated with the maximal distance between the primary tumor and the lymph node or with clinical parameters was significantly correlated with higher risk of DM or death, respectively.

Implications for patient care: These parameters may be used to tailor individualized treatment.

ACKNOWLEDGMENTS

No specific grant from funding agencies in the public, commercial, or not-for-profit sectors was received. The LTSI/INSERM/U1099 (Rennes, France) and the Cancer Institute (Rennes) supported the study.

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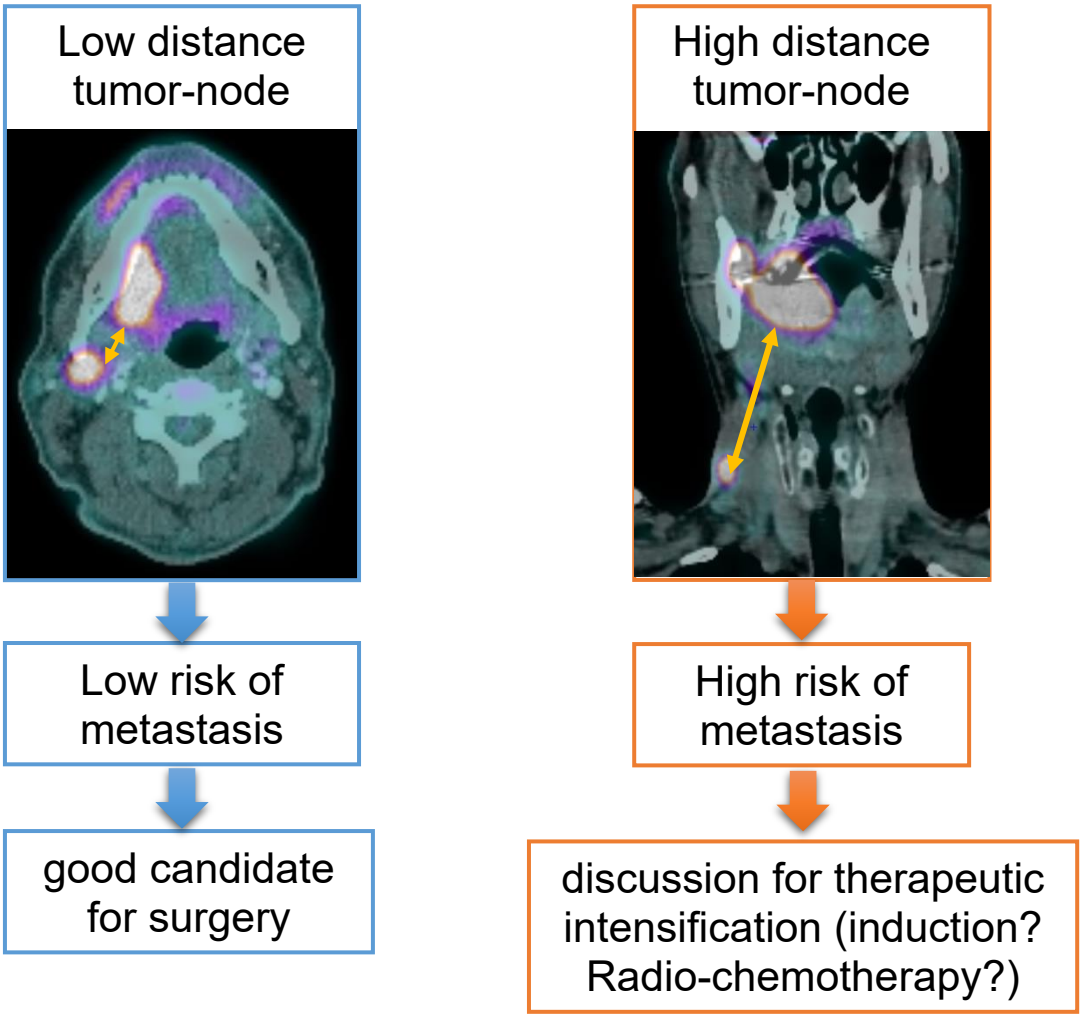
Graphical Abstract



Figures

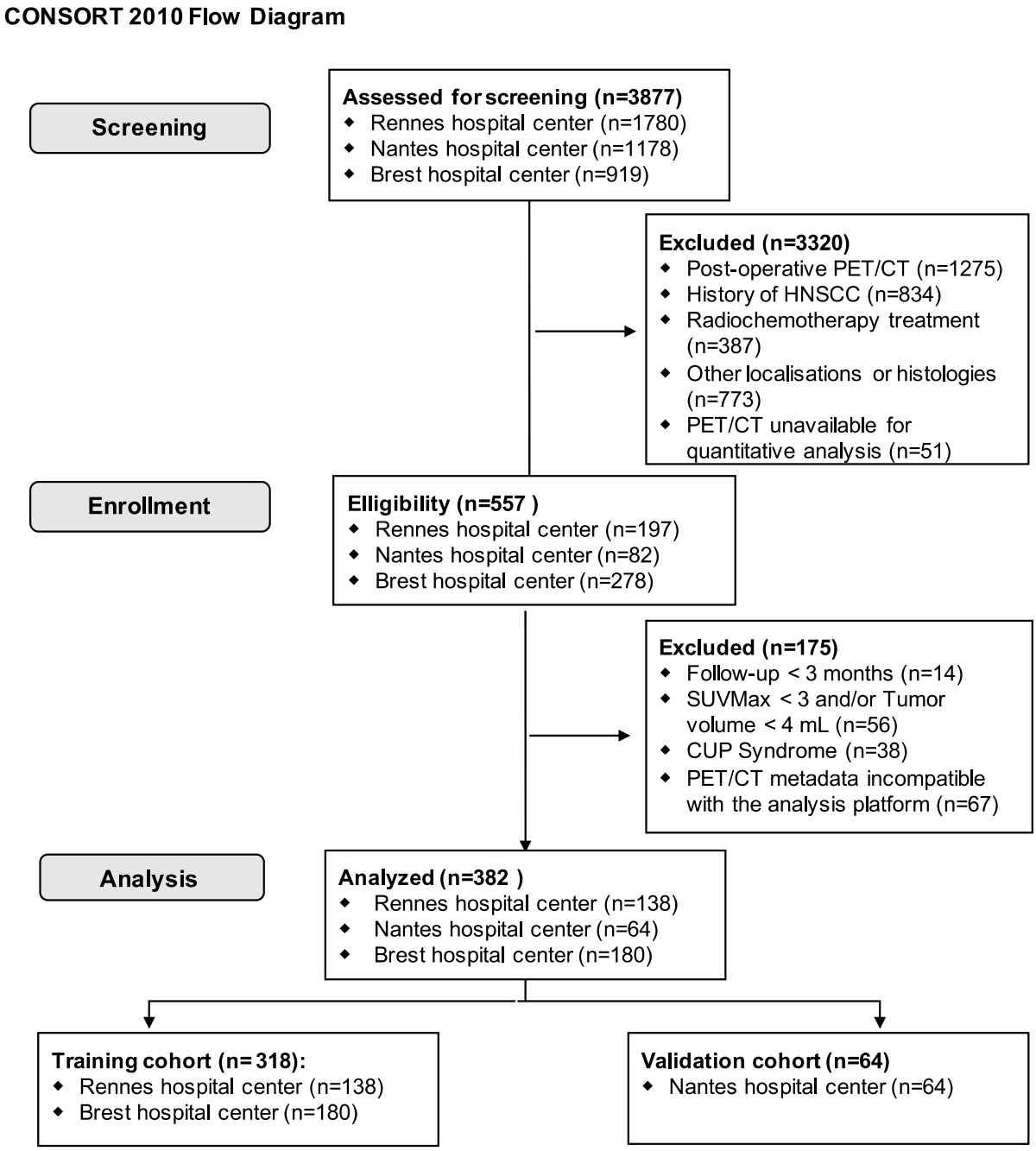


Figure 1: Flow Chart

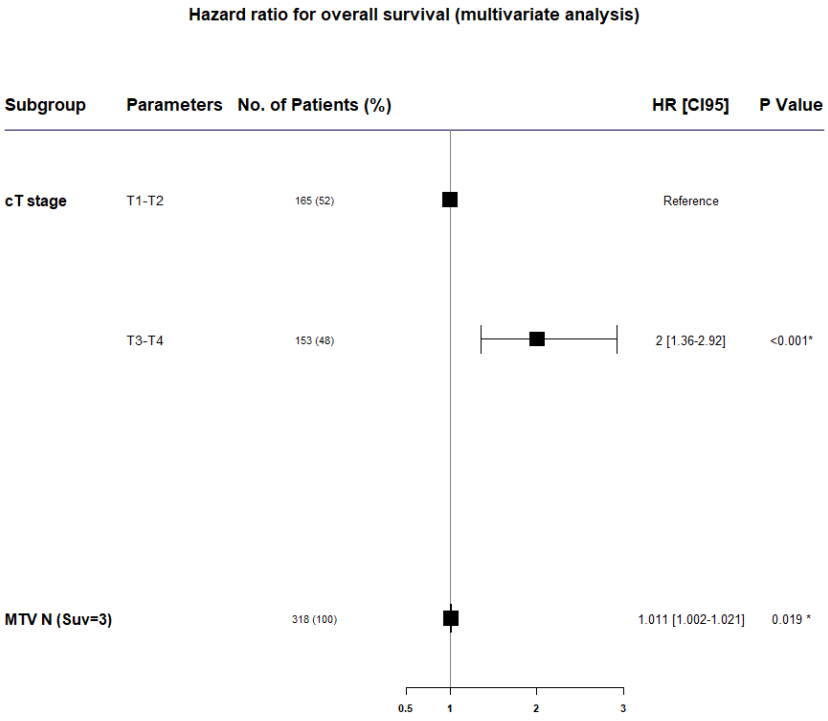


Figure 2: Parameters significatively impacting the OS in the training cohort in multivariable analysis (number of deaths = 116, c-index=0.64)

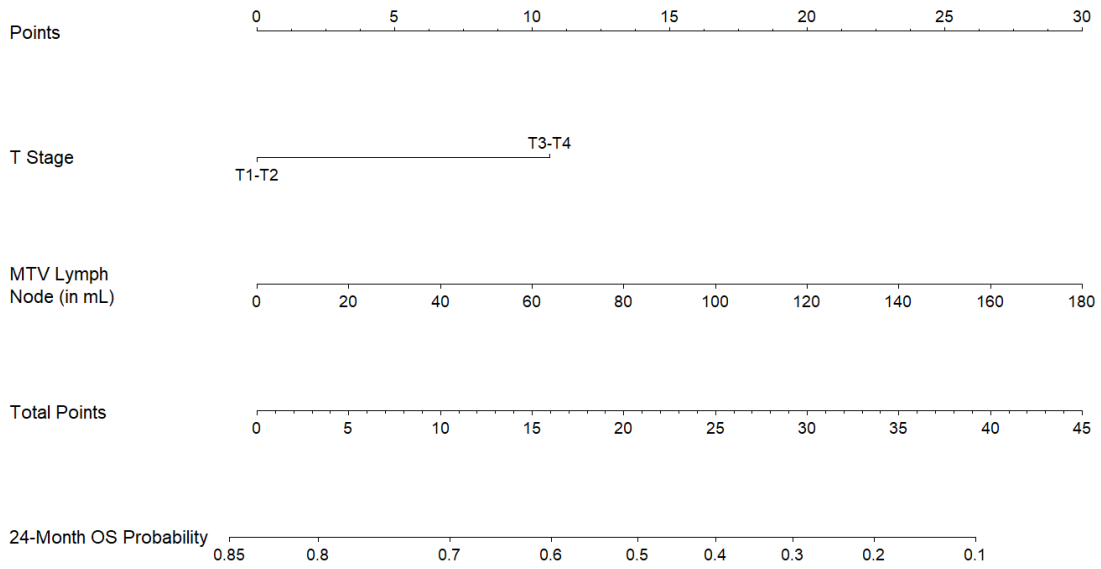


Figure 3: Nomogram to predict the OS at 24 months. For each PET-parameter, the corresponding points is

obtained by drawing a line upward from the corresponding values to the 'Points' line. The total points for each patient is obtained by summing the points for each of the individual factors in the nomogram and is plotted on the 'Total points' line. A line is drawn down to read the corresponding predictions of 24-months OS.

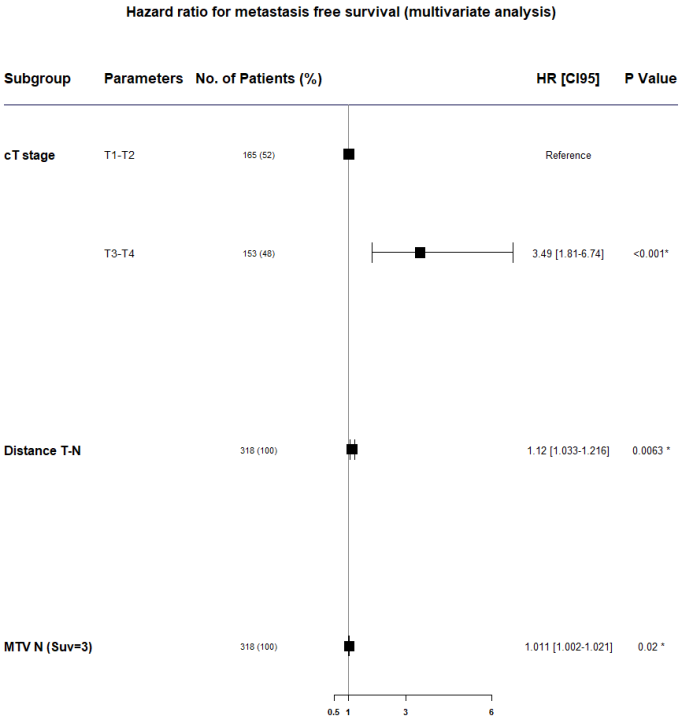


Figure 4: Parameters significatively impacting the DMFS in the training cohort in multivariable analysis (number of patients with distant metastasis = 51, c-index=0.76)

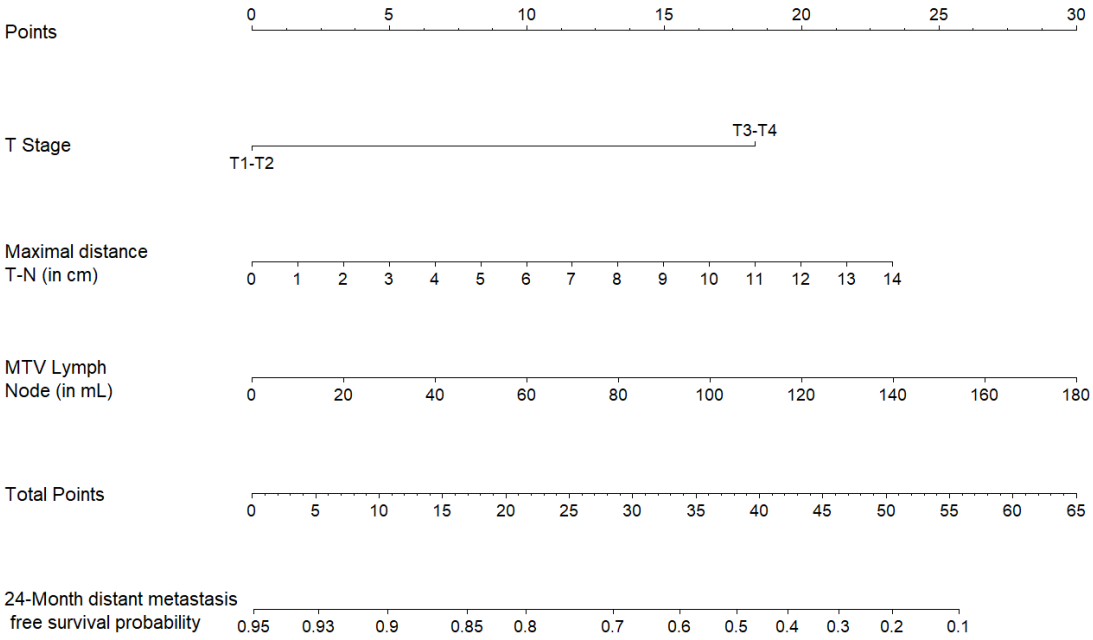


Figure 5: Nomogram to predict the DMFS at 24 months.

Tables

Table 1: Univariable Cox analyses for OS in the training cohort (number of deaths=116)

Parameters	HR [95% CI]	c-index	p-value
Clinical parameters			
Age (in years)	1.011 [0.99;1.03]	0.509	0.28
Gender			
Female	ref		
Male	1.51 [0.89;2.6]	0.53	0.12
Tobacco			
No	ref		
Yes	2.13 [1.11;4.1]	0.52	0.02
Alcohol			
No	ref		
Yes	1.34 [0.99;4.1]	0.55	0.1
PS			
0-1	ref		
2	2.65 [1.07;6.5]	0.52	0.03
T classification			
cT1-cT2	ref		
cT3-cT4	2.01 [1.4;2.9]	0.61	0.003
N classification			
cN0	ref		
cN1	1.19 [0.69;2.05]	0.53	0.5
cN2	1.13 [0.75;1.7]	0.53	0.5
cN3	2.32[0.83;6.45]	0.53	0.1
AJCC staging			
I	ref		
II	2.17[0.89;5.3]	0.575	0.09
III	3.11[1.36;7.1]	0.575	0.007
IV	2.59[1.24;5.4]	0.575	0.01
Tumor site			
Oral cavity	ref		
Hypopharynx	1.81[1.08 ; 3.03]	0.55	0.02
Larynx	1.29[0.78 ; 2.15]	0.55	0.3
Oropharynx	1.26[0.75 ; 2.12]	0.55	0.4
Metabolic data*			
Tumor metabolic data			
SUV Max	1.004 [0.988;1.021]	0.54	0.58
MTV T (23% of SUVmax)	1.02 [1.01;1.03]	0.64	<0.001
MTV T (SUV = 2.5)	1.01[1.001;1.014]	0.61	0.038
TLG T (21% of SUVmax)	1.001[1.00;1.01]	0.61	0.04
TLG T (SUV = 1.5)	1.001 [1.000;1.002]	0.61	0.038
Node metabolic data			
MTV N (21% of SUVmax)	1.007 [1.001;1.013]	0.566	0.014
MTV N (SUV = 3.0)	1.010 [1.000;1.019]	0.563	0.014
TLG N (21% of SUVmax)	1.001 [1.000;1.002]	0.564	0.02
TLG N (SUV = 3.0)	1.001 [1.000;1.002]	0.551	0.036
Maximal tumor-node distance	1.04 [0.99;1.1]	0.57	0.08
dst_TBarycenterN	1.08 [1.01,1.16]	0.58	0.02

*For PET parameters, data are given only for absolute and relative thresholds with the highest c-index.

PS = Performance Status, dst_TBarycenterN= distance between the tumor and the barycenter of all node metastases

Table 2: Univariable Cox analyses for DMFS in the training cohort (number of patients with DM=51)

Parameters	HR [95%CI]	c-index	p-value
Clinical parameters			
Age (in years)	1.020 [0.990;1.051]	0.540	0.197
Gender			
Female	ref		
Male	1.861 [0.738;4.694]	0.532	0.188
Tobacco			
No	ref		
Yes	2.112 [0.760;5.874]	0.533	0.152
Alcohol			
No	ref		
Yes	1.111 [0.634;1.945]	0.517	0.714
PS			
0-1	ref		
2	0.963 [0.133 ;6.988]	0.502	0.970
T classification			
cT1-cT2	Ref		
cT3-cT4	6.795 [1.981;23.334]	0.660	0.002
N classification			
cN0			ref
cN1	1.432 [0.530;3.874]	0.638	0.479
cN2	3.034 [1.518;6.088]	0.638	0.002
cN3	3.851 [1.072;13.827]	0.638	0.039
AJCC staging			
I	Ref		
II	1.389 [0.196 ;9.865]	0.595	0.742
III	3.116 [0.647 ;15.006]	0.595	0.156
IV	4.513 [1.089 ;18.708]	0.595	0.038
Tumor site			
Oral cavity	ref		
Hypopharynx	1.946 [0.914;4.140]	0.578	0.084
Larynx	0.875 [0.374;2.049]	0.578	0.759
Oropharynx	1.094 [0.507;2.361]	0.578	0.818
Metabolic data			
Tumor metabolic data			
SUV Max	1.040 [1.010;1.072]	0.617	0.009
MTV T (15% of SUVmax)	1.026 [1.016;1.036]	0.709	< 0.0001
MTV T (SUV = 4.0)	1.033 [1.020;1.046]	0.720	0.0000005
TLG T (21% of SUVmax)	1.003 [1.002;1.005]	0.720	< 0.0001
TLG T (SUV = 4.0)	1.003 [1.002;1.004]	0.714	0.0000008
Node metabolic data			
MTV N (21% of SUVmax)	1.011 [1.000;1.021]	0.694	0.04
MTV N (SUV = 3.0)	1.016 [1.007;1.026]	0.693	0.0002
TLG N (21% of SUVmax)	1.002 [1.001;1.003]	0.698	0.004
TLG N (SUV = 3.0)	1.002 [1.001;1.026]	0.694	0.0006
Distance parameters			
Maximal tumor-node distance	1.177 [1.092;1.269]	0.679	0.00002
dst_MTVweightedSumDistTN	1.002 [1.001;1.004]	0.696	0.00003
dst_MTVweightedMaxDistTN	1.003 [1.001;1.006]	0.68	0.01

dst_MTVweightedSumDistTN= sum of distances weighted by the respective MTV of the metastases,
dst_MTVweightedMaxDistTN = metastasis remoteness weighted by the MTV of the corresponding metastasis

Supplemental Table 1: PET-CT acquisition parameters of the 3 Hospital Centers

	Rennes Hospital Center	Nantes Hospital Center	Brest Hospital Center
Injection	4 MBq/kg of FDG[d] (0.0001Ci/kg)	3 MBq/kg of FDG[d] (0.00008Ci/kg)	3 MBq/kg of FDG[d] (0.00008Ci/kg)
Fasting period before injection (mean, hours)	4	5	6
Uptake time (mean, minutes)	60	60	60
Imaging system	Discovery PET/CT[e] imaging-system or Siemens Biograph 6 True Point PET/CT scanner (Siemens Healthineers©, Erlangen, Germany)	Biograph-mCT™ 40 or 64 imaging system (Siemens Healthineers©, Erlangen, Germany)	Biograph-mCT™ 40 or 64 imaging system
Reconstruction	OSEM[a] (2 iterations, 28 subsets) Iterative fully 3D (Discovery ST)	OSEM[a] with PSF[b] correction and TOF[c] information	OSEM[a] with PSF[b] modeling and TOF[c] acquisition capabilities method

[a]OSEM: Ordered Subset Expectation Maximization , [b]PSF: Point spread function, [c]TOF: Time-of-Flight, [d]FDG : Fluorodeoxyglucose (IBA Molecular Imaging, Saclay, France)., [e]PET/CT: Positron Emission Tomography/Computed Tomography

Supplemental Table 2: Patient, tumor, treatment and follow-up characteristics for the training and validation cohorts

Characteristics	Training cohort (N = 318 patients)	Validation cohort (N = 64 patients)	p-value*
Patients			
Age, mean (SD)	61.51 (9.33)	58.86 (10.82)	0.071
Gender, n (%)			0.272
Male	260 (82.07)	56 (87.50)	
Female	58 (17.93)	8 (12.50)	
Smoking status (yes, n (%))	269 (84.59)	55 (85.94)	0.744
Amount of tobacco (pack-year, SD)	23.34 (24.73)	18.84 (21.42)	0.176
Alcohol consumption (yes, n(%))	166 (52.20)	29 (45.31)	0.326
Amount of alcohol consumed (g, SD)	21.59 (41.18)	14.41 (28.38)	0.092
Performance Status, n (%)			0.564
0-1	309 (97.17)	63 (98.44)	
2	9 (2.83)	1 (1.56)	
Tumor			
Tumor site, n (%)			0.777
Oral cavity	106 (33.33)	20 (31.25)	
Oropharynx	77 (24.21)	18 (28.13)	
Larynx	74(23.27)	12 (18.75)	
Hypopharynx	61 (19.18)	14 (21.88)	
cT classification, n(%)			0.016
T1	80 (25.16)	8 (12.50)	
T2	85 (27.04)	14 (21.88)	
T3	43 (13.52)	17 (26.56)	
T4	110 (34.28)	25 (39.06)	
cN classification, n(%)			0.065
N0	144 (45.28)	17 (26.56)	
N1	49 (15.41)	9 (14.06)	
N2	118 (31.11)	35 (54.69)	
N3	7 (2.20)	3 (4.69)	
Staging AJCC, n (%)			0.034
I	44 (13.84)	2 (3.13)	
II	38 (12.26)	4 (6.25)	
III	51 (16.04)	12 (18.75)	
IV	185 (57.86)	46 (71.88)	
pT classification, n (%)			0.016
pT1	72 (22.64)	7 (10.64)	
pT2	94 (29.56)	13 (20.31)	
pT3	47 (14.78)	17 (26.56)	
pT4	105 (33.02)	27 (42.19)	
pN classification, n (%)			0.028
pN0	151 (47.48)	19 (29.69)	
pN1	42 (13.21)	10 (15.63)	
pN2a	15 (4.71)	3 (4.69)	
pN2b	68 (21.38)	21 (32.81)	
pN2c	33 (10.38)	7 (10.94)	
pN3	9 (2.83)	4 (6.25)	
Lymph node involvement, mean number (SD)	1.70 (3.47)	2.05 (6.44)	0.217
Extracapsular extension, n (%)	94 (29.56)	26 (40.63)	0.082
Negative surgical margin, n(%)	252 (79.25)	34 (53.13)	0.001
Perineural invasion, n (%)	94 (29.56)	26 (40.63)	0.082
Vascular invasion, n (%)	48 (15.09)	27 (42.19)	0.001
p16 status, n(%)			0.004
Yes	16 (5.03%)	10 (15.63)	
No	21 (6.60%)	7 (10.94)	
Not applicable/available	281(88.37%)	47 (73.44)	
Tumor volume in mL (SD)			
Primitive tumor	28.90 (29.18)	34.93 (28.33)	0.130
Total (tumor and nodes)	45.18 (49.07)	53.72 (42.32)	0.195
Treatment			
Type of surgery			0.267
Oropharyngectomy	80 (25.16)	18 (28.13)	
Glossectomy	30 (9.43)	5 (7.81)	
Mandibulectomy I or NI or maxillectomy	73 (22.96)	15 (23.43)	
Partial laryngectomy	44 (13.84)	3 (4.69)	
Total laryngectomy/ pharyngolaryngectomy	91 (28.61)	23 (35.94)	

Radiotherapy postsurgery, n (%)	210 (66.04)	54 (84.38)	0.004
Concomitant chemotherapy, n(%)	120 (37.74)	38 (59.38)	0.006
Follow-up			
Distant Metastasis, n(%)	51 (16.04)	10 (15.63)	0.934
Deaths, n(%)	116 (36.48)	19 (29.69)	0.299

SD = standard deviation, 95% CI = 95% confidence interval, AJCC = American Joint Committee on Cancer, NI = Noninterruptive, I = Interruptive

*= Mann-Whitney test for continuous variables, chi² for dichotomous variables, or Fisher exact test when the frequency was small and log-rank test for survival analysis.

Supplemental Table 3: Results of the Cox model bootstrap validation (1000 resampling) for overall survival

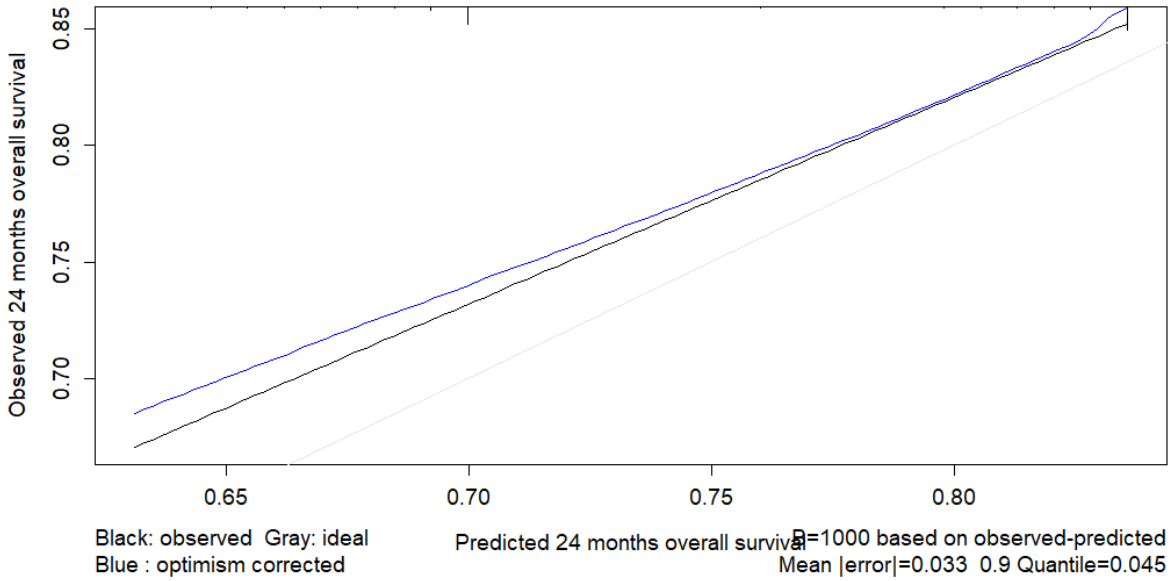
Parameters	**HR[95% CI]**	**P value of the parameter**	**c-index**
Stage T		<0.001	
T1-T2	Ref.		
T3-T4	2.01 [1.13 ; 4.65]		0.63
MTV N (SUV = 3.0)	1.01 [1 ;1.18]	0.03	

HR = Hazard ratio, 95% CI = 95% confidence interval

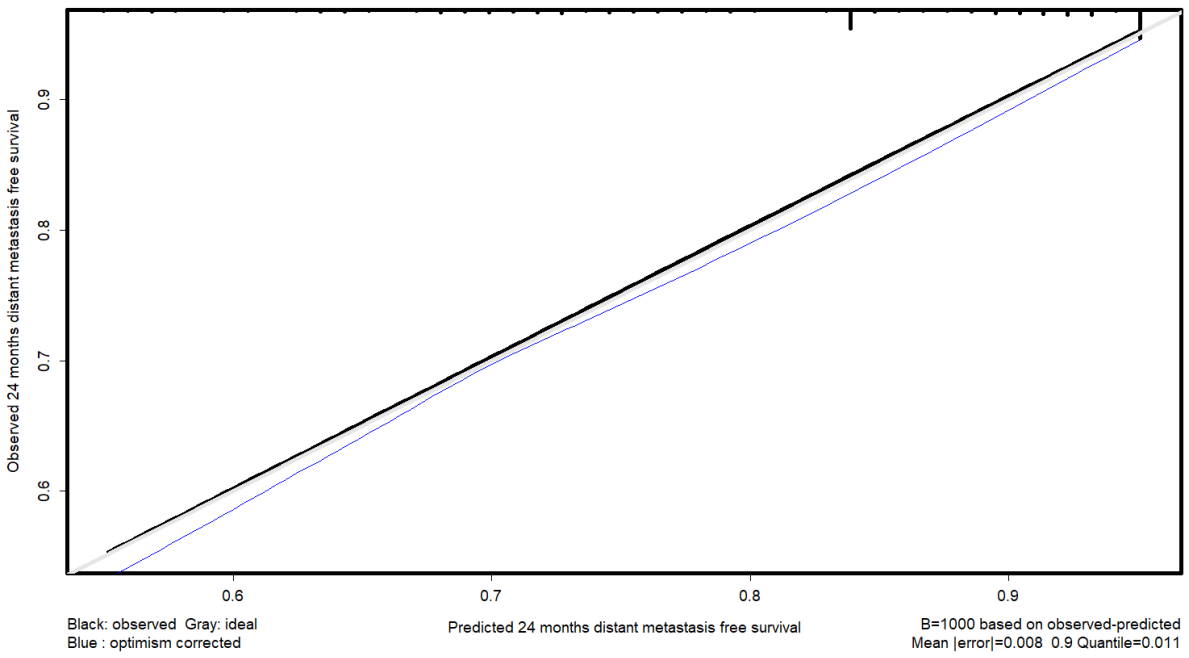
Supplemental Table 4: Results of the Cox model bootstrap validation (1000 resampling) for distant metastasis

Parameters	**HR[95% CI]**	**P value of the parameter**	**c-index**
Stage T		<0.001	
T1-T2	Ref.		
T3-T4	3.59 [1.9-7.6]		0.74
MTV N (SUV = 3.0)	1.01 [1.0;1.02]	0.055	
Distance max TN	1.12 [1.03;1.21]	0.007	

HR = Hazard ratio, 95% CI = 95% confidence interval, NS=Not significant, Distance max TN = Maximal tumor-node distance



Supplemental Figure 1: Internal calibration of the final OS model for the training cohort at 24 months. The gray line is the ideal model, the black line is the observedsurvival, and the blue-dotted line is the predicted survival corrected to avoid overfitting.



Supplemental Figure 2: Internal calibration of the final DMFS nmodel for the training cohort at 24 months. The gray line is the ideal model, the black line is the observed survival and the blue-dotted line is the predicted survival corrected to avoid overfitting.