



HAL
open science

Influence of postoperative radiotherapy target volumes in unilateral head and neck carcinoma of unknown primary: A multicentric study using propensity score

Esteban Brenet, Pierre Philouze, Camille Schiffler, Pascal Pommier, Carole Crozes, Nazim Benzerdjeb, Elodie Monchet, Camille Boulagnon-Rombi, Jean Ton Van, Fabien Podeur, et al.

► To cite this version:

Esteban Brenet, Pierre Philouze, Camille Schiffler, Pascal Pommier, Carole Crozes, et al.. Influence of postoperative radiotherapy target volumes in unilateral head and neck carcinoma of unknown primary: A multicentric study using propensity score. *Radiotherapy & Oncology*, 2021, 160, pp.1-8. 10.1016/j.radonc.2021.04.002 . hal-03216680

HAL Id: hal-03216680

<https://hal.univ-reims.fr/hal-03216680>

Submitted on 9 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Influence of postoperative radiotherapy target volumes in unilateral head and neck carcinoma of unknown primary: a multicentric study using propensity score

Authors :

BRENET, Esteban, MD, Head and Neck surgery Department, Centre Hospitalo

Universitaire Reims, Reims, France

PHILOUZE, Pierre, MD-PhD, Head and Neck surgery Department, Centre Hospitalo

Universitaire Lyon Sud, Lyon, France

SCHIFFLER, Camille, MsC , biostatistics Department, Centre Léon Bérard, Lyon, France

POMMIER Pascal, MD-PhD, Radiotherapy Department, Centre Léon Bérard, Lyon, France

CROZES Carole, MD, Pathological Anatomy Department, Centre Léon Bérard, Lyon,

France

BENZERDJEB, Nazim, MD-PhD, Pathological Anatomy Department, Centre Hospitalo

Universitaire Lyon Sud, Lyon, France

MONCHET Elodie, MD, Head and Neck Surgery Department, Centre Oscar Lambret, Lille,

France

BOULAGNON-ROMBI Camille, PD-PhD, Pathological Anatomy Department, Centre

Hospitalo Universitaire Reims, Reims, France

TON VAN Jean, MD, Head and Neck Department, Centre Oscar Lambret, Lille, France

PODEUR Fabien, MD, Oncologic Surgery Department, Centre Léon Bérard, Lyon,

SERVAGI-VERNAT Stéphanie, MD-PhD, radiotherapy department, Institut Godinot,

Reims, France

LIEM Xavier, MD, Radiotherapy department, Centre Oscar Lambret, Lille, France

MEROL Jean-Claude, MD, Head and Neck Department, Centre hospitalo Universitaire
Reims, Reims, France

CERUSE Philippe, MD-PhD, Head and Neck surgery Department, Centre Hospitalo
Universitaire Lyon Sud, Lyon,

SERRE Anne Agathe, MD, Radiotherapy Department, Centre Léon Bérard, Lyon, France

CHABAUD Sylvie, MsC, biostatistics department, Centre Léon Bérard, Lyon, France

JULIERON Morbize, MD, Head and Neck Surgery Department, Centre Oscar Lambret,
Lille, France

DENEUVE Sophie, MD, Oncologic Surgery Department, Centre Léon Bérard, Lyon,

CORRESPONDING AUTHOR :

Dr DENEUVE Sophie

Centre Léon Bérard

28 rue Laennec

LYON - FRANCE

Sophie.deneuve@lyon.unicancer.fr

Phone number: 00-33-478782946

Fax: 00-33-478782701

FINANCIAL DISCLOSURE AND PRODUCTS

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

ACKNOWLEDGEMENTS TO:

- The authors want to thank Professor Vincent Gregoire, head of the Radiotherapy department at the Léon Bérard Center in Lyon for its relevant critical review and modifications of this manuscript.

Keywords: carcinoma unknown primary, head and neck, postoperative radiotherapy, propensity score matching

Abstract: 245 words

Manuscript: 2969 words

FINANCIAL DISCLOSURE AND PRODUCTS

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

ACKNOWLEDGEMENTS TO:

- The authors want to thank Professor Vincent Gregoire, head of the Radiotherapy department at the Léon Bérard Center in Lyon for his relevant critical review and modifications of this manuscript.

Keywords: carcinoma unknown primary, head and neck, postoperative radiotherapy, propensity score matching

Abstract: 245 words

Manuscript: 3046 words

Abstract:

Objective: To compare the impact of two radiation modalities on loco-regional control, survival and tumour emergence, after node dissection for an unilateral head and neck carcinoma of unknown primary (HNCUP).

Materials and methods: This is a multicentric retrospective study of 138 patients with unilateral HNCUP treated between 2002 and 2017. The absence of primary tumour was assessed by a systematic panendoscopy and positron emission tomography. Neck dissection was initially performed for all patients. Radiation Therapy was delivered on ipsilateral lymph node areas in 62 cases (44%: UL-RT group) and on bilateral lymph node areas and the entire pharyngeal mucosa in 77 cases (56%: COMP-RT group). Impact of radiation modalities on locoregional control and overall survival was assessed using propensity score matching method in order to balance baseline characteristics between the two groups.

Results: The population included 80.4% men, 80.4% smokers, 32.6% P16 positive tumours and 71.0% extracapsular extension. After a median follow-up of 5 years, the locoregional control rate was 80.3% in the UL-RT group and 75.3% in the COMP-RT group ($p = 0.688$). The corresponding rate of contralateral lymph node recurrence was 0% versus 2.6% ($p = 0.503$) and the rate of tumour emergence was 11.5% versus 9.1% ($p = 0.778$). No significant difference was observed between the UL-RT and the COMP-RT groups for overall survival ($p = 0.9516$), specific survival ($p = 0.4837$) or tumour emergence ($p = 0.9034$).

Conclusion: UL-RT seems to provide similar outcomes as COMP-RT in unilateral HNCUP post-operative management.

Introduction:

In about 3–5% of patients with malignant epithelial tumours, no primary tumour is found despite extensive investigations, leading to the diagnosis of "Cancer of Unknown Primary" (CUP) (1). The most common histology encountered in Head and Neck (HN) CUP (HNCUP) patients is squamous cell carcinoma (SCC) in 66–77%, followed by undifferentiated carcinoma and adenocarcinoma (2). Lymph node metastases are usually located in the upper two-thirds of the neck (levels II-III according to Robbins) mainly deriving from HNSCC (3). Although lymph node metastases usually occur unilaterally, they may occur bilaterally in about 10% of cases (4).

Over the last few years, there has been a decrease in the incidence of HNCUP, due to a more accurate diagnosis of the primary tumour by means of a thorough optic endoscopy of the pharynx and larynx, esophagogastroduodenoscopy and advanced imaging technology, especially positron emission tomography scan (PET-CT) (5).

Due to the relative rarity of this cancer, there is substantial heterogeneity in the treatment of HNCUP. Although treatment with surgery alone or exclusive radiotherapy has been proposed, neck dissection followed by post-operative radiotherapy seems to be the most consensual approach (6–8). Nevertheless, recommended post-operative irradiation volumes vary from ipsilateral lymph node irradiation to bilateral and pan mucosal irradiation (9,10), in consideration of whether a hypothetical primary tumour should be treated or not.

However, the morbidity of mucosal irradiation may be high, decreasing the quality of life of relatively young patients. No randomized or prospective studies are currently available to specifically support one of these approaches, and treatment is mainly based on non-randomized evidence and institutional policies.

The purpose of this study was to compare the outcome of unilateral nodal irradiation alone (UL-RT) versus bilateral irradiation and pharyngeal pan-mucosa irradiation (COMP-RT) after cervical node dissection of a HNCUP, in selected patients, with no primary tumour on PET-CT and panendoscopy. Locoregional control, primary emergence and survival were the main endpoints.

Materials and Methods:

Patients and Diagnosis:

The data of all patients treated in 4 reference centers between January, 1st 2002 and December, 31th 2017 were analyzed retrospectively.

Inclusion criteria were unilateral HNCUP, histologically proven SCC with no mucosal tumour detectable on panendoscopy and 18FDG PET-CT and patients eligible for surgical treatment. Exclusion criteria were distant metastases at time of diagnosis, prior history of skin or HN SCC or cervical radiotherapy.

The panendoscopy evaluating the upper aerodigestive tract was combined with rigid oesophagoscopy under general anesthesia with biopsy of any suspicious mucosal sites macroscopically visualized or guided by PET-CT. No patient underwent prophylactic tonsillectomy.

P16 status was assessed on formalin-fixed, paraffin-embedded sections from neck dissection tissues by immunohistochemistry. P16 positivity was defined as strong and diffuse nuclear and cytoplasmic staining in more than 70% of tumor cells.

EBV status was assessed retrospectively on formalin-fixed, paraffin-embedded sections from neck dissection tissues by In Situ Hybridization for all available samples (125/138 patients).

Treatment modalities:

Surgery:

Patients underwent initial ipsilateral selective neck dissection of levels II, III, and IV with curative intent. Modified radical neck dissection was realized when tumour invasion made it necessary. Staging used the AJCC pTNM 8th edition, 2017.

Radiotherapy and chemotherapy:

Post-operative treatment was based on each center local policies.

Two centers delivered postoperative radiotherapy only on the ipsilateral neck (UL-RT Group) and the remaining 2 centers delivered a postoperative comprehensive radiotherapy (COMP-RT group), including bilateral neck and panmucosal irradiation (naso-, oro-, and hypopharyngeal regions).

The external beam radiation therapy was delivered either by 3D conformal RT or by Intensity Modulated RT (IMRT). Many patients have been treated sequentially but the integrated boost technique has been applied to some patients in recent years.

For both centers, pathologically involved node level(s) received with equivalent dose in 2 Gy fractions (EQD2, $\alpha/\beta=10$) 50 to 60 Gy in 25 or 30 fractions (five fractions per week) or 66Gy in 33 fractions if extra-capsular spread. The prophylactic irradiation delivered 50 to 54 Gy in 25 or 27 fractions (EQD2) (five fractions per week) in other homolateral nodes level (including systematically homolateral levels II, III, IVa and levels Ib and V if level II was involved) (11). In the COMP-RT group, the entire pharyngeal mucosa and the contralateral nodes (levels II, III, IVa) also received the prophylactic irradiation.

Unless contraindicated due to the patient's general condition, a concurrent Chemotherapy was associated in case of extra-capsular spread, or N3 stage.

Statistical analysis

Baseline characteristics of patients were described between Groups (UL-RT and COMP-RT) using Wilcoxon test for the continuous variables and Fischer exact test for the qualitative variables, due to low sample size.

Overall survival (OS) was defined as the time from the first day of radiotherapy to death from any cause or censored at the last follow-up. Specific survival (SS) was defined as the time from the first day of radiotherapy to death due to disease or censored in case of death for intercurrent cause or at the last follow-up. Locoregional-relapse free survival (LRFS) was defined from the first day of radiotherapy to the date of disease progression or censored at the last follow-up. Survival functions were calculated using the Kaplan-Meier method. Survival distributions were compared between the two arms using a log-rank test.

SAS, version 9.4, was used for all statistical analyses.

Propensity score : (12,13).

A propensity score was built to adjust for differences between groups to reduce biases in the estimation of treatment effects associated with non-random observational data. The expected probability of receiving unilateral irradiation was calculated for each patient by fitting a multivariate logistic regression model including following covariates: Gender (male / female), Tobacco use (yes / no), Alcohol consumption (none / occasional / abuse / *missing*), P16 status (yes / no / *missing*), Nodal status (pN1 / pN2a / pN2b / pN3), Side of disease (left / right), and Extracapsular extension (yes / no).

We used the inverse probability of treatment weighted (IPTW) method with stabilized weights (14) in order to balance the observable characteristics. For alcohol consumption and P16 status, we built a group with missing data to keep these cases in the propensity score. To control the balance between the groups after IPTW, we measured the standardized difference, here always lower than 10% (supplemental data 1).

Ethics approval:

In accordance with French laws, this retrospective study on medical records has been authorized by the CNIL (Commission Nationale Informatique et Libertés - authorization number 111 85 23).

Results:

The characteristics of all 138 patients and tumours and the treatment modalities are summarized in Table 1.

Median age at diagnosis was 61 (range 41 - 92). Median follow-up time was 60 months (range 1.8-162.5 months).

Sixty-one patients were in the UL-RT Group and 77 patients were in the COMP-RT Group.

All patients were treated with a conformal technique: conventional (3D-CRT) in 13%, or intensity modulated (IMRT) in 87% without any statistically difference between the 2 groups. Due to extracapsular extension, 98 patients (71.0%) received a concomitant chemotherapy: 38 patients in the UL-RT Group (62.3%) and 58 in the COMP-RT Group (75.3%) ($p=0.135$).

Eighty patients (58.0%) did not express P16, while 45 patients (32.6%) had P16 positive immunostaining.

Hybridation in situ was negative for 125/138 patients, and missing for 13 patients.

Patients' characteristics differ between groups at baseline: Patients treated with UL-RT were less addicted (tobacco or chronic alcohol consumption), had lower N stage or no extracapsular extension, and were more often P16 positive.

Data with regional control, recurrence and distant metastasis are detailed in table 2.

Overall Survival (OS) did not differ significantly between the 2 groups with or without the use of the propensity score. After IPTW , the 2-year and 5-year OS rates were 76.0% (confidence interval (CI) 95%: [60.0-88.3]) versus 80.0% (CI 95%: [67.4-88.2]) and 55.8% (CI 95%: [35.9-71.8]) versus 57.6% (CI 95%: [42.8-69.9]) respectively after UL-RT and COMP-RT (HR = 0.982, CI 95%: [0.548 - 1.760], $p=0.9516$) (Figure 1).

Locoregional recurrence free survival (LRFS) did not differ significantly between the 2 groups with or without the use of the propensity score. After IPTW , the 2-year and 5-year LRFS rates were 88.0% (CI 95%: [71.4-95.2]) and 65.9% (CI 95%: [41.3-82.2]) respectively after UL-RT versus 79.0% (CI 95%: [65.7-87.6]) and 72.7% (CI 95%: [56.5-83.7]) respectively after COMP-RT (HR = 0.950, CI 95%: [0.416 - 2.168], $p=0.9034$) (Figure 2).

29 patients developed distant metastases during the follow-up period (21.0%):

- 10 in the UL-RT Group (16.4%)

- 19 in the COMP-RT Group (24.7%)

SS did not differ significantly between the 2 groups with or without the use of the propensity score. After IPTW, the 2-year and 5-year SS rates were 80.9% (confidence interval (CI) 95%: [64.8-90.1]) and 66.4% (CI 95%: [43.8-81.6]) respectively after UL-RT versus 80.9% (CI 95%: [68.3-88.9]) and 63.9% (CI 95%: [48.5-75.7]) respectively after COMP-RT (HR = 0.765, CI 95%: [0.361 - 1.620], $p=0.4837$) (Figure 3).

The P16 status significantly influenced overall survival of the whole cohort (Figure 4). The 2-year and 5-year OS rates were 72% (CI 95%: [60-81]) and 60% (CI 95%: [47-71]) respectively in patients P16 negative versus 98% (CI 95%: [85-100]) and 87% (CI 95%: [67-95]) respectively in patients P16 positive (logrank p -value= 0.0003; HR = 5.48, CI 95%: [1.93-15.55]).

Among the P16+ patients, 3/25 experienced an emerging tumour in the UL-RT group and 0/20 in the COMP-RT group ($p=0.24$). 1/45 patient experienced metastatic relapse 22 months after the end of the COMP-RT without concurrent chemotherapy and died 18 months later.

The 2 patients with contralateral lymph node recurrence in the COMP-RT group were P16 negative.

The TNM status according to the 8th edition significantly influenced overall survival of the whole cohort (supplemental data 2)

Discussion:

Our study about 138 patients diagnosed with HNCUP with systematic PET-CT and panendoscopy did not find any significant difference neither in OS, SS or LRFS nor in tumour emergence treated by UL- RT versus COMP-RT after neck dissection.

HNCUP are heterogeneous pathologic conditions with no optimal treatment strategy. Neck dissection followed by post-operative radiotherapy is generally accepted as a standard approach, whereas the question of the extent of radiotherapy (both sides of the neck and the pharyngeal mucosa or ipsilateral neck node areas) is still unresolved (15). In the absence of a randomized prospective study, the available retrospective studies, often with small numbers of patients, are subject to sampling bias. Several studies showed that limiting the target volume to ipsilateral nodes also reduced the toxicity (16–20).

Hypothesis:

Currently, the main hypothesis explaining the presentation of HNCUP is the existence of an undetected primary tumour despite a full assessment. The lymphadenopathy location indicates that the tumour should be located in the upper aero-digestive tract mucosa and especially in the oropharynx, numerous HNCUP appearing to be P16+. The primary tumour would consist of slow growing tumour clones, maintained in a latent state by patient's immune system. Migrating to the draining lymph nodes, clones escape the immune system and grow rapidly leading to HNCUP (21).

A second hypothesis suggests that the primary tumour completely involutes because of inborn errors (22), or by immune system pressure (21,23), as the tumour process continues in lymphadenopathy. Spontaneous disappearance of cancer without any therapeutic intervention occurs more frequently in melanoma but is also described in HNSCC: causal factors are operative trauma, infection, vaccination, immunological factors, blood transfusion and various endocrine factors (24).

A last hypothesis suggests that HNCUP represents a cancer group in its own right, where the primary tumour mimics a lymph node metastasis, or affects a lateral neck cyst (22,25).

Depending on the pathophysiological hypothesis adopted, diagnostic and therapeutic strategies differ. If there is a small, latent primary, improving detection techniques and treating the tumour is mandatory. On the other hand, if the primary tumour involuted or is the lymphadenopathy itself, treating the pharyngeal mucosa seems irrelevant.

Neck relapse:

In our series, the neck relapse rate was similar in the 2 groups, 8.2% after UL-RT and 16.9% after COMP-RT (p=NS). Median neck relapse rate ranging from 31 to 63% after UL-RT group (26–31) and from 18 to 49% in COMP-RT group (26–28,31–38) are poorer.

More precisely, in our study no contralateral neck node recurrences occurred in the UL-RT group (0%) and 2 occurred in the COMP-RT group (2.6%) without significant difference. On the contrary, some authors reported a significantly higher control rate in the contralateral side of the neck for the COMP-RT group than for the UL-RT group (86% versus 56% respectively, p=0.03) (28), however without any significant difference in survival.

In another series (26) 224 patients received a COMP-RT and 26 patients received a UL-RT with various techniques: combining all relapses above the clavicle, patients treated with UL-RT had a relative risk of 1.9 (p = 0.05) compared with those receiving COMP-RT. However, multivariate analyses found no difference in the rates of mucosal primary emergence, nodal failure nor survival, and only a few patients had a PET-CT. A more recent cohort study of 297 patients comparing uni- vs bilateral nodal irradiation concluded that bilateral nodal irradiation yielded non-significant better nodal control rates, without any difference in SS and was associated with higher rates of severe toxicity (39). This study nevertheless suffers from having poorly comparable groups and only 82.1% PET-CT performed.

Recently, multiple institutions decrease the treatment of CUP patients from adjuvant bilateral radiotherapy including the pharyngeal mucosa to adjuvant ipsilateral radiotherapy alone (17,18,40). Ipsilateral radiotherapy resulted in contralateral relapse rates between 4% and 9% and if it occurred, the contralateral disease was most often curable and did not affect the mortality rates (41,42).

Primary tumour emergence:

The most frequent sites reported being oropharynx, nasopharynx, oral cavity and larynx (26,43), the purpose of panmucosal irradiation is to treat an hypothetical occult tumour and thus prevent the emergence of the primary tumour. Indeed, several authors (28,29) reported a mucosal primary emergence rate significantly higher in the UL-RT group compared to the COMP-RT group. A meta-analysis covering studies from 1986 to 2015 (6) also concluded that the addition of pan-mucosal irradiation to neck node irradiation reduced the rate of primary tumour emergence. However, in all these studies, a lot of enrolled patients did not undergo previous PET-CT. Yet it has been showed that PET-CT can improve the detection of 25% of occult tumours, especially small oropharyngeal SCC (44). Besides, the absence of

PET-CT have been proved to be associated with poor survival (39).

In the era of PET-CT, other authors (16,17) also found that abandoning mucosal irradiation does not increase tumour emergences. Similarly, Marcial-Vega et al. (31) did not show a significant impact of target volume definition on primary emergence rate and 5-year survival on 80 patients.

In our study where the diagnosis of HNCUP by PET-CT was an inclusion criteria, 14 primary tumours occurred (10.1%), without the irradiation volume affecting significantly the frequency of their occurrence. Indeed, despite mucosal irradiation, 7 primary tumours emerged in our COMP-RT group (9.1%). Thus mucosal irradiation seems not fully efficient in eradicating microscopic disease, while it prevents to combine radiotherapy to surgery in case of relapse. Interestingly in our study, despite P16+ patients have a better survival than P16-, P16+ HNCUP treated with exclusive ipsilateral irradiation did not show more tumour emergence than HNCUP P16- or HNCUP P16+ treated with COMP-RT. However, the limited number of P16 + patients (N=45) limits the statistical power of these observations.

Type of relapse and survival:

The most frequent type of relapse in our study were distant metastases (24.7%), neck node recurrence (13.0%), followed by the emergence of a primary tumour (10.1%). Numerous studies showed that the most frequent site of recurrence is neck node failures followed by distant metastases, the risk of neck or distant relapse being reported as twice the risk of primary tumour onset (26,27,45). This highlights the small impact of the potential emergence of a primary tumour on the OS and LRFS.

The incidence of distant metastases, varies in series from 11% to 33% (32,46), and raises the question of the interest for including chemotherapy in the treatment strategy. Although its use is supported by some authors, there is no clear cut evidence supporting the systematic use of chemotherapy in patients affected by HNCUP (47). For some authors patients receiving radiochemotherapy by N2b–N3 nodal status showed a lower frequency of distant metastases (48). However, for others chemotherapy was not beneficial for survival or local control rate (15,49), while significantly higher rates of acute and late toxicities were observed (49).

Limitations:

One limitation of our study was its retrospective nature. The sampling bias generated by the heterogeneity of the two groups regarding gender, smoking, alcohol consumption, P16 status, N3 status and extracapsular effraction was reduced by using propensity score by IPTW method.

However, hidden bias due to latent variables may remain after matching, since these patients were not randomized

Conclusions:

The strengths of our study include: a systematic initial PET-CT coupled with panendoscopy, a uniform surgical treatment with systematic primary neck dissection, and an important number of patients allowing performing PSM.

After using PSM, we still did not observe any significant difference in OS, SS and LRFS between the two groups. It is thus possible that the improvement of HNCUP diagnostic techniques and especially the realization of a PET-CT scan systematically coupled with panendoscopy will allow the selection of true HNCUP for which the treatment of the primary tumour does not improve the prognosis.

References :

1. Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. *Lancet Lond Engl*. 14 avr 2012;379(9824):1428-35.
2. Koivunen P, Laranne J, Virtaniemi J, Bäck L, Mäkitie A, Pulkkinen J, et al. Cervical Metastasis of Unknown Origin: A Series of 72 Patients. *Acta Otolaryngol (Stockh)*. 1 janv 2002;122(5):569-74.
3. Doty JM, Gossman D, Kudrimoti M, Valentino J, Arnold S, Spring PM. Analysis of unknown primary carcinomas metastatic to the neck: diagnosis, treatment, and outcomes. *J Ky Med Assoc*. févr 2006;104(2):57-64.
4. Rödel RMW, Matthias C, Blomeyer BD, Wolff HA, Jung K, Christiansen H. Impact of distant metastasis in patients with cervical lymph node metastases from cancer of an unknown primary site. *Ann Otol Rhinol Laryngol*. sept 2009;118(9):662-9.
5. Hatten KM, O'Malley BW, Bur AM, Patel MR, Rassekh CH, Newman JG, et al. Transoral Robotic Surgery-Assisted Endoscopy With Primary Site Detection and Treatment in Occult Mucosal Primaries. *JAMA Otolaryngol-- Head Neck Surg*. 01 2017;143(3):267-73.
6. Liu X, Li D, Li N, Zhu X. Optimization of radiotherapy for neck carcinoma metastasis from unknown primary sites: a meta-analysis. *Oncotarget*. 29 nov 2016;7(48):78736-46.
7. Amsbaugh MJ, Yusuf M, Gaskins J, Silverman C, Potts K, Bumpous J, et al. Neck dissection for unknown cancer of the head and neck in the era of chemoradiation. *Am J Otolaryngol*. oct 2017;38(5):588-92.
8. Shoushtari A, Saylor D, Kerr K-L, Sheng K, Thomas C, Jameson M, et al. Outcomes of patients with head-and-neck cancer of unknown primary origin treated with intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 1 nov 2011;81(3):e83-91.
9. Strojan P, Ferlito A, Medina JE, Woolgar JA, Rinaldo A, Robbins KT, et al. Contemporary management of lymph node metastases from an unknown primary to the neck: I. A review of diagnostic approaches. *Head Neck*. janv 2013;35(1):123-32.
10. Strojan P, Ferlito A, Langendijk JA, Corry J, Woolgar JA, Rinaldo A, et al. Contemporary management of lymph node metastases from an unknown primary to the neck: II. a review of therapeutic options. *Head Neck*. févr 2013;35(2):286-93.
11. Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. janv 2014;110(1):172-81.
12. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 15 oct 1998;17(19):2265-81.
13. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1 avr 1983;70(1):41-55.
14. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health J Int Soc Pharmacoeconomics Outcomes Res*. avr 2010;13(2):273-7.
15. Ligez A, Gentil J, Créhange G, Montbarbon X, Pommier P, Peignaux K, et al. Impact of target volumes and radiation technique on loco-regional control and survival for patients with unilateral cervical lymph node metastases from an unknown primary. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. déc 2009;93(3):483-7.

16. Perkins SM, Spencer CR, Chernock RD, Haughey BH, Nussenbaum B, Adkins DR, et al. Radiotherapeutic management of cervical lymph node metastases from an unknown primary site. *Arch Otolaryngol Head Neck Surg.* juill 2012;138(7):656-61.
17. Fakhrian K, Thamm R, Knapp S, Molls M, Pigorsch S, Haller B, et al. Radio(chemo)therapy in the management of squamous cell carcinoma of cervical lymph nodes from an unknown primary site. A retrospective analysis. *Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al.* janv 2012;188(1):56-61.
18. Straetmans J, Vent J, Lacko M, Speel E-J, Huebbers C, Semrau R, et al. Management of neck metastases of unknown primary origin united in two European centers. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg.* janv 2015;272(1):195-205.
19. Richards TM, Bhide SA, Miah AB, Del Rosario L, Bodla S, Thway K, et al. Total Mucosal Irradiation with Intensity-modulated Radiotherapy in Patients with Head and Neck Carcinoma of Unknown Primary: A Pooled Analysis of Two Prospective Studies. *Clin Oncol R Coll Radiol G B.* 2016;28(9):e77-84.
20. Johansen J, Petersen H, Godballe C, Loft A, Grau C. FDG-PET/CT for detection of the unknown primary head and neck tumor. *Q J Nucl Med Mol Imaging Off Publ Ital Assoc Nucl Med AIMN Int Assoc Radiopharmacol IAR Sect Soc Of.* oct 2011;55(5):500-8.
21. Varadhachary GR. Carcinoma of unknown primary origin. *Gastrointest Cancer Res GCR.* nov 2007;1(6):229-35.
22. van de Wouw AJ, Jansen RLH, Speel EJM, Hillen HFP. The unknown biology of the unknown primary tumour: a literature review. *Ann Oncol Off J Eur Soc Med Oncol.* févr 2003;14(2):191-6.
23. Challis GB, Stam HJ. The spontaneous regression of cancer. A review of cases from 1900 to 1987. *Acta Oncol Stockh Swed.* 1990;29(5):545-50.
24. Cervinkova M, Kucerova P, Cizkova J. Spontaneous regression of malignant melanoma - is it based on the interplay between host immune system and melanoma antigens? *Anticancer Drugs.* 2017;28(8):819-30.
25. Fishkin BG, Spiegelberg HL. Cervical lymph node metastasis as the first manifestation of localized extramedullary plasmacytoma. *Cancer.* oct 1976;38(4):1641-4.
26. Grau C, Johansen LV, Jakobsen J, Geertsen P, Andersen E, Jensen BB. Cervical lymph node metastases from unknown primary tumours. Results from a national survey by the Danish Society for Head and Neck Oncology. *Radiother Oncol J Eur Soc Ther Radiol Oncol.* mai 2000;55(2):121-9.
27. Colletier PJ, Garden AS, Morrison WH, Goepfert H, Geara F, Ang KK. Postoperative radiation for squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site: outcomes and patterns of failure. *Head Neck.* déc 1998;20(8):674-81.
28. Reddy SP, Marks JE. Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. *Int J Radiat Oncol Biol Phys.* 1 mars 1997;37(4):797-802.
29. Weir L, Keane T, Cummings B, Goodman P, O'Sullivan B, Payne D, et al. Radiation treatment of cervical lymph node metastases from an unknown primary: an analysis of outcome by treatment volume and other prognostic factors. *Radiother Oncol J Eur Soc Ther Radiol Oncol.* juin 1995;35(3):206-11.
30. Glynn-Jones RG, Anand AK, Young TE, Berry RJ. Metastatic carcinoma in the cervical lymph nodes from an occult primary: a conservative approach to the role of

- radiotherapy. *Int J Radiat Oncol Biol Phys.* févr 1990;18(2):289-94.
31. Marcial-Vega VA, Cardenes H, Perez CA, Devineni VR, Simpson JR, Fredrickson JM, et al. Cervical metastases from unknown primaries: radiotherapeutic management and appearance of subsequent primaries. *Int J Radiat Oncol Biol Phys.* oct 1990;19(4):919-28.
 32. Strojan P, Anicin A. Combined surgery and postoperative radiotherapy for cervical lymph node metastases from an unknown primary tumour. *Radiother Oncol J Eur Soc Ther Radiol Oncol.* oct 1998;49(1):33-40.
 33. Harper CS, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Cancer in neck nodes with unknown primary site: role of mucosal radiotherapy. *Head Neck.* déc 1990;12(6):463-9.
 34. Bataini JP, Rodriguez J, Jaulerry C, Brugere J, Ghossein NA. Treatment of metastatic neck nodes secondary to an occult epidermoid carcinoma of the head and neck. *The Laryngoscope.* sept 1987;97(9):1080-4.
 35. Maulard C, Housset M, Brunel P, Rozec C, Ucla L, Delanian S, et al. [Primary cervical lymph nodes of epidermoid type. Results of a series of 123 patients treated by the association surgery-radiotherapy or irradiation alone]. *Ann Oto-Laryngol Chir Cervico Faciale Bull Soc Oto-Laryngol Hopitaux Paris.* 1992;109(1):6-13.
 36. Davidson BJ, Spiro RH, Patel S, Patel K, Shah JP. Cervical metastases of occult origin: the impact of combined modality therapy. *Am J Surg.* nov 1994;168(5):395-9.
 37. Lefebvre JL, Coche-Dequeant B, Van JT, Buisset E, Adenis A. Cervical lymph nodes from an unknown primary tumor in 190 patients. *Am J Surg.* oct 1990;160(4):443-6.
 38. Nguyen C, Shenouda G, Black MJ, Vuong T, Donath D, Yassa M. Metastatic squamous cell carcinoma to cervical lymph nodes from unknown primary mucosal sites. *Head Neck.* févr 1994;16(1):58-63.
 39. Pflumio C, Troussier I, Sun XS, Salleron J, Petit C, Caubet M, et al. Unilateral or bilateral irradiation in cervical lymph node metastases of unknown primary? A retrospective cohort study. *Eur J Cancer Oxf Engl 1990.* 2019;111:69-81.
 40. Podeur F, Pommier P, Crozes C, Monchet E, Ton Van J, Roux P-E, et al. Management of unilateral head and neck carcinoma of unknown primary: Retrospective analysis of the impact of postoperative radiotherapy target volumes. *Head Neck.* févr 2020;42(2):302-11.
 41. Aslani M, Sultanem K, Voung T, Hier M, Niazi T, Shenouda G. Metastatic carcinoma to the cervical nodes from an unknown head and neck primary site: Is there a need for neck dissection? *Head Neck.* juin 2007;29(6):585-90.
 42. Nieder C, Gregoire V, Ang KK. Cervical lymph node metastases from occult squamous cell carcinoma: cut down a tree to get an apple? *Int J Radiat Oncol Biol Phys.* 1 juill 2001;50(3):727-33.
 43. Erkal HS, Mendenhall WM, Amdur RJ, Villaret DB, Stringer SP. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. *Int J Radiat Oncol Biol Phys.* 1 mai 2001;50(1):55-63.
 44. Lee JR, Kim JS, Roh J-L, Lee JH, Baek JH, Cho K-J, et al. Detection of occult primary tumors in patients with cervical metastases of unknown primary tumors: comparison of (18)F FDG PET/CT with contrast-enhanced CT or CT/MR imaging-prospective study. *Radiology.* mars 2015;274(3):764-71.
 45. Fernández JA, Suárez C, Martínez JA, Llorente JL, Rodrigo JP, Alvarez JC. Metastatic squamous cell carcinoma in cervical lymph nodes from an unknown primary

- tumour: prognostic factors. Clin Otolaryngol Allied Sci. avr 1998;23(2):158-63.
46. Medini E, Medini AM, Lee CK, Gapany M, Levitt SH. The management of metastatic squamous cell carcinoma in cervical lymph nodes from an unknown primary. Am J Clin Oncol. avr 1998;21(2):121-5.
47. de Braud F, al-Sarraf M. Diagnosis and management of squamous cell carcinoma of unknown primary tumor site of the neck. Semin Oncol. juin 1993;20(3):273-8.
48. Rödel RMW, Matthias C, Blomeyer BD, Wolff HA, Jung K, Christiansen H. Impact of Distant Metastasis in Patients with Cervical Lymph Node Metastases from Cancer of an Unknown Primary Site: Ann Otol Rhinol Laryngol. 1 sept 2009
49. Chen AM, Farwell DG, Lau DH, Li B-Q, Luu Q, Donald PJ. Radiation therapy in the management of head-and-neck cancer of unknown primary origin: how does the addition of concurrent chemotherapy affect the therapeutic ratio? Int J Radiat Oncol Biol Phys. 1 oct 2011;81(2):346-52.

	Irradiation		All N=138	p value
	UL-RT* group N=61	COMP-RT** group N=77		
Age (years)				
Median (min; max)	60 (44; 92)	62 (41; 85)	61 (41; 92)	0.89
Sex n (%)				
Men	45 (73.8)	66 (85.7)	111 (80.4)	0.088
Women	16 (26.2)	11 (14.3)	27 (19.6)	
Tabacco use n (%)				
No	15 (24.6)	7 (9.1)	22 (15.9)	0.017
Yes	43 (70.5)	68 (88.3)	111 (80.4)	
Missing	3 (4.9)	2 (2.6)	5 (3.6)	
Alcohol consumption n (%)				
No	19 (31.1)	24 (31.2)	43 (31.2)	0.010
Occasionnal	19 (31.1)	14 (18.2)	33 (23.9)	
Chronic	7 (11.5)	26 (33.8)	33 (23.9)	
Missing	16 (26.2)	13 (16.9)	29 (21.0)	
P16 n (%)				
Negative	30 (49.2)	50 (64.9)	80 (58.0)	0.062
Positive	25 (41.0)	20 (26.0)	45 (32.6)	
Missing	6 (9.8)	7 (9.1)	13 (9.4)	
Nodal status (AJCC TNM 8th edition) n (%)				
pN1	27 (44.3)	21 (27.3)	48 (34.8)	0.024
pN2a	7 (11.5)	4 (5.2)	11 (8.0)	
pN2b	2 (3.3)	3 (3.9)	5 (3.6)	
pN3a	0 (0.0)	1 (1.3)	1 (0.7)	
pN3b	18 (29.5)	41 (53.2)	59 (42.8)	
Missing	7 (11.5)	7 (9.1)	14 (10.1)	
Extracapsular extension n (%)				
No	25 (41.0)	14 (18.2)	39 (28.3)	0.004
Yes	35 (57.4)	63 (81.8)	98 (71.0)	
Missing	1 (1.6)	0 (0.0)	1 (0.7)	
Type of cervical lymph node dissection n (%)				
Functional	39 (63.9)	15 (19.5)	54 (39.1)	0.74
Radical and modified radical	22 (34.5)	62 (80.5)	76 (60.2)	
cervical lymph node dissection				
Missing	1 (1.6)	0 (0.0)	1 (0.7)	
Median delay surgery-RT	46	48		
Min	27	23		
Max	90	72		
Irradiation technique n (%)				
IMRT***	46 (75.4)	74 (96.1)	120 (87.0)	
Conformational 3D	15 (24.6)	2 (2.6)	17 (12.3)	
Missing	0 (0.0)	1 (1.3)	1 (0.7)	
Concomitant chemotherapy n (%)				
No	23 (37.7)	19 (24.7)	42 (30.4)	
Yes	38 (62.3)	58 (75.3)	96 (69.6)	

*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy *** Intensity Modulated RT

Table 1. Tumors and patients characteristics and treatment modalities

	Irradiation				All	p value
	UL-RT* group		COMP-RT** group			
	N = 61		N = 77		N = 138	
Loco-regional recurrence n (%)	12	(19.7)	19	(24.7%)	31	(22.5) 0.542
Mucosal tumor emergence n (%)	7	(11.5)	7	(9.1)	14	(10.1) 0.778
Cervical lymph node recurrence n (%)						
Homolateral only	5	(8.2)	10	(13.0)	15	(10.9)
Controlateral only	0	(0.0)	2	(2.6)	2	(1.4)
Bilateral	0	(0.0)	1	(1.3)	1	(0.7)
Metastases n (%)	10	(16.4)	19	(24.7)	29	(21.0) 0.295

*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy

Table 2. Regional control, recurrence and distant metastasis

FIGURES' LEGEND

Figure 1. Overall survival curves with regard to irradiation volumes after propensity score matching

*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy

Figure 2. Locoregional recurrence free survival with regard to irradiation volumes after propensity score matching

*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy

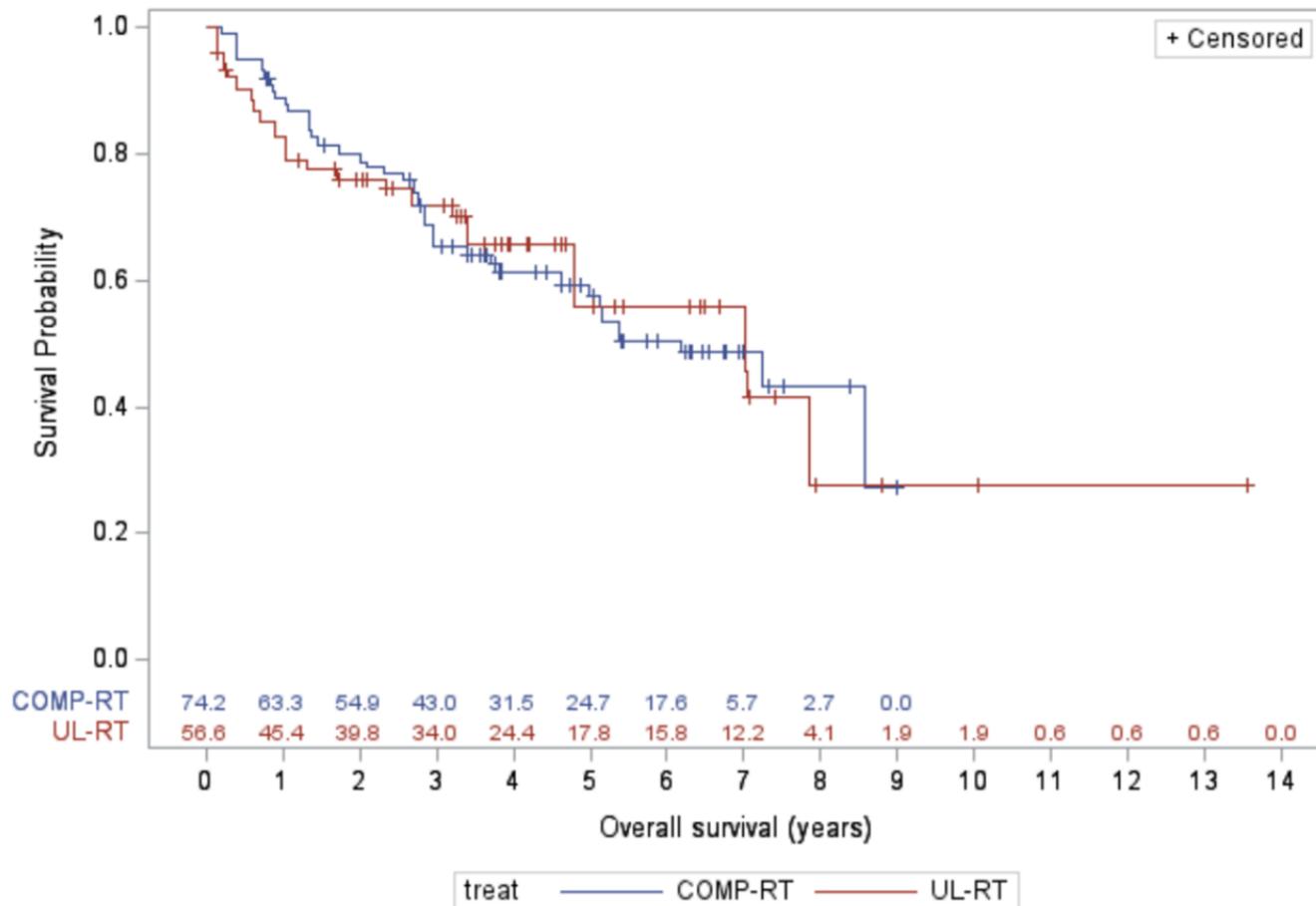
Figure 3. Specific survival curves with regard to irradiation volumes after propensity score matching

*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy

Figure 4. Specific survival curves with regard to P16 status in the whole cohort regardless the received treatment.

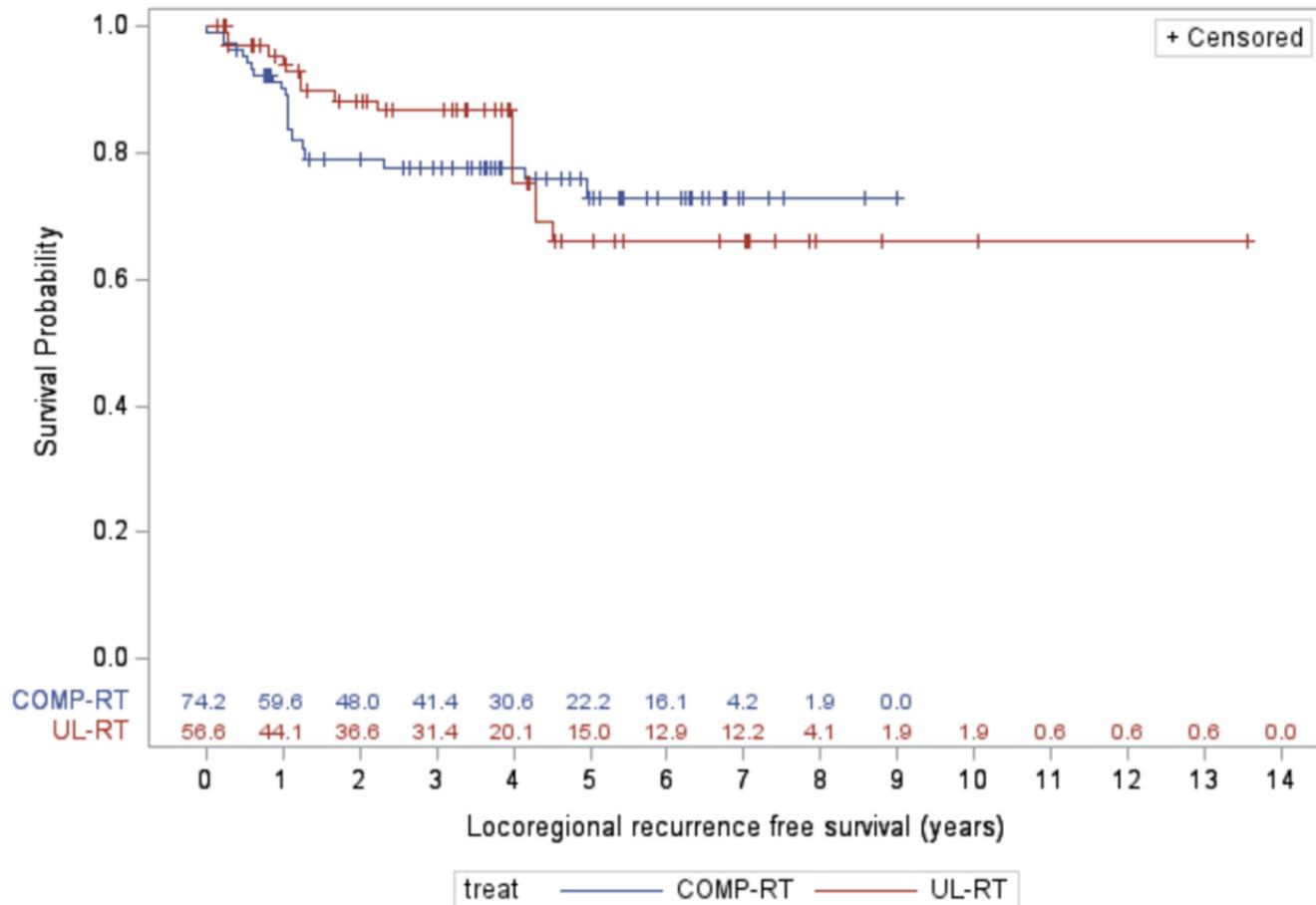
Adjusted Product-Limit Survival Estimates

With Number of Subjects at Risk



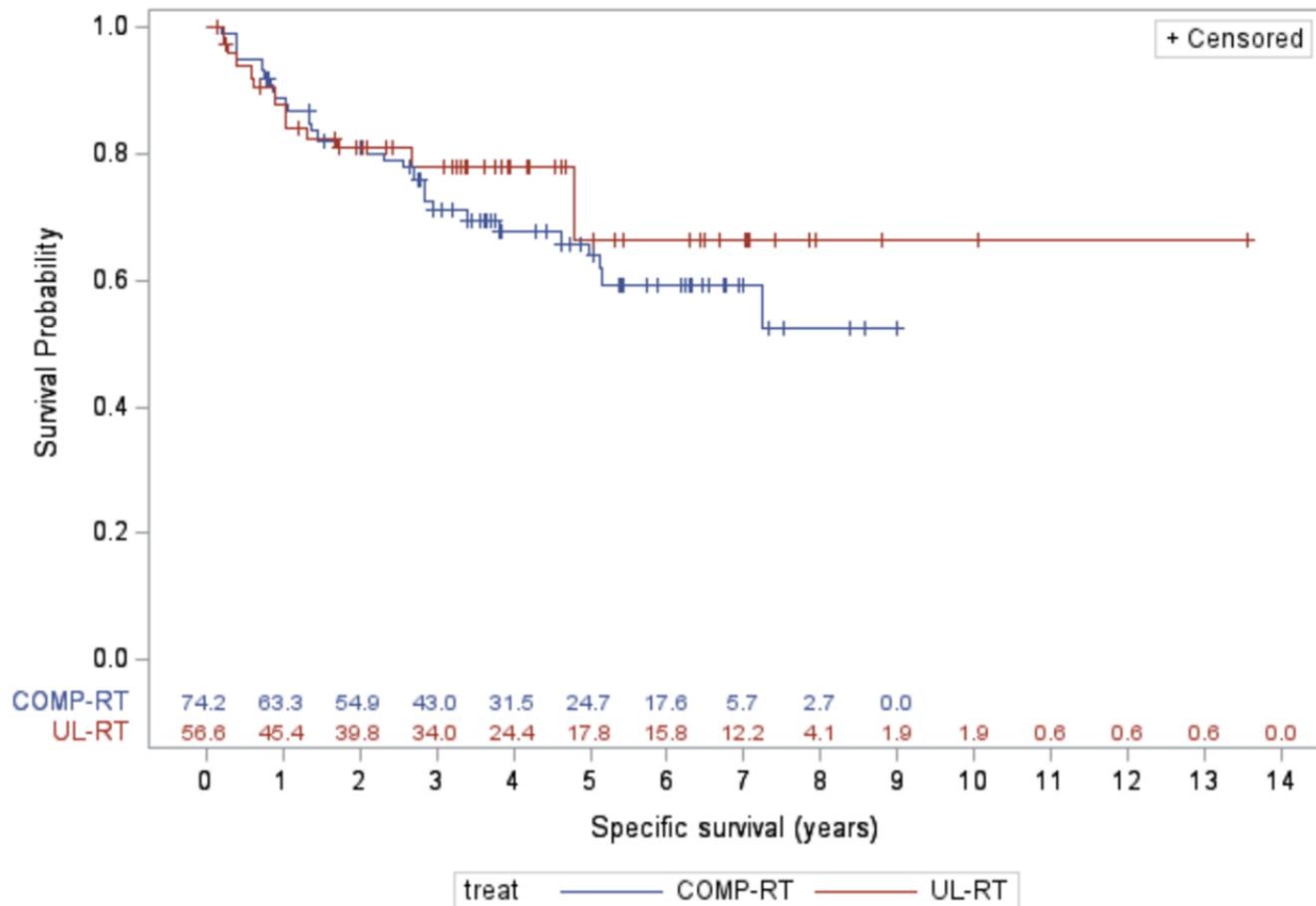
Adjusted Product-Limit Survival Estimates

With Number of Subjects at Risk



Adjusted Product-Limit Survival Estimates

With Number of Subjects at Risk



Product-Limit Survival Estimates

With Number of Subjects at Risk

