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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 hypothetic 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.

Hibridation 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 found 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 ispilateral 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 propensy 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.

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	Irradiation		All	*p* value
	UL-RT* group	COMP-RT** group		
	N=61	N=77	N=138	
Age (years)				
Median (min; max)	60 (44; 92)	62 (41; 85)	61 (41; 92)	0.89
Sexe 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)	
Radical and modified radical cervical lymph node dissection	22 (34.5)	62 (80.5)	76 (60.2)	
Missing	1 (1.6)	0 (0.0)	1 (0.7)	
Median delay surgery-RT	46	48		0.74
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 reccurence 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

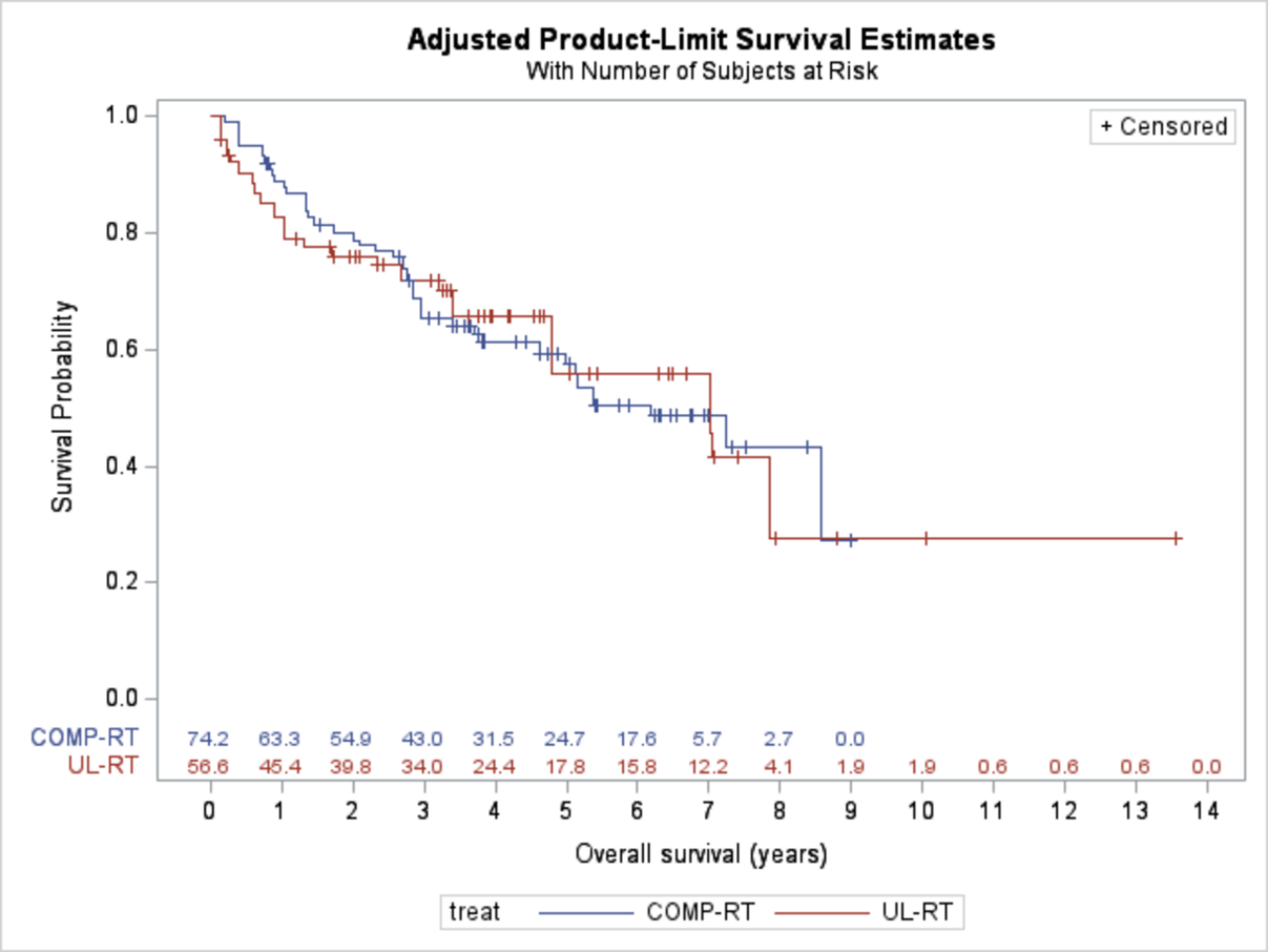
FIGURES' LEGEND

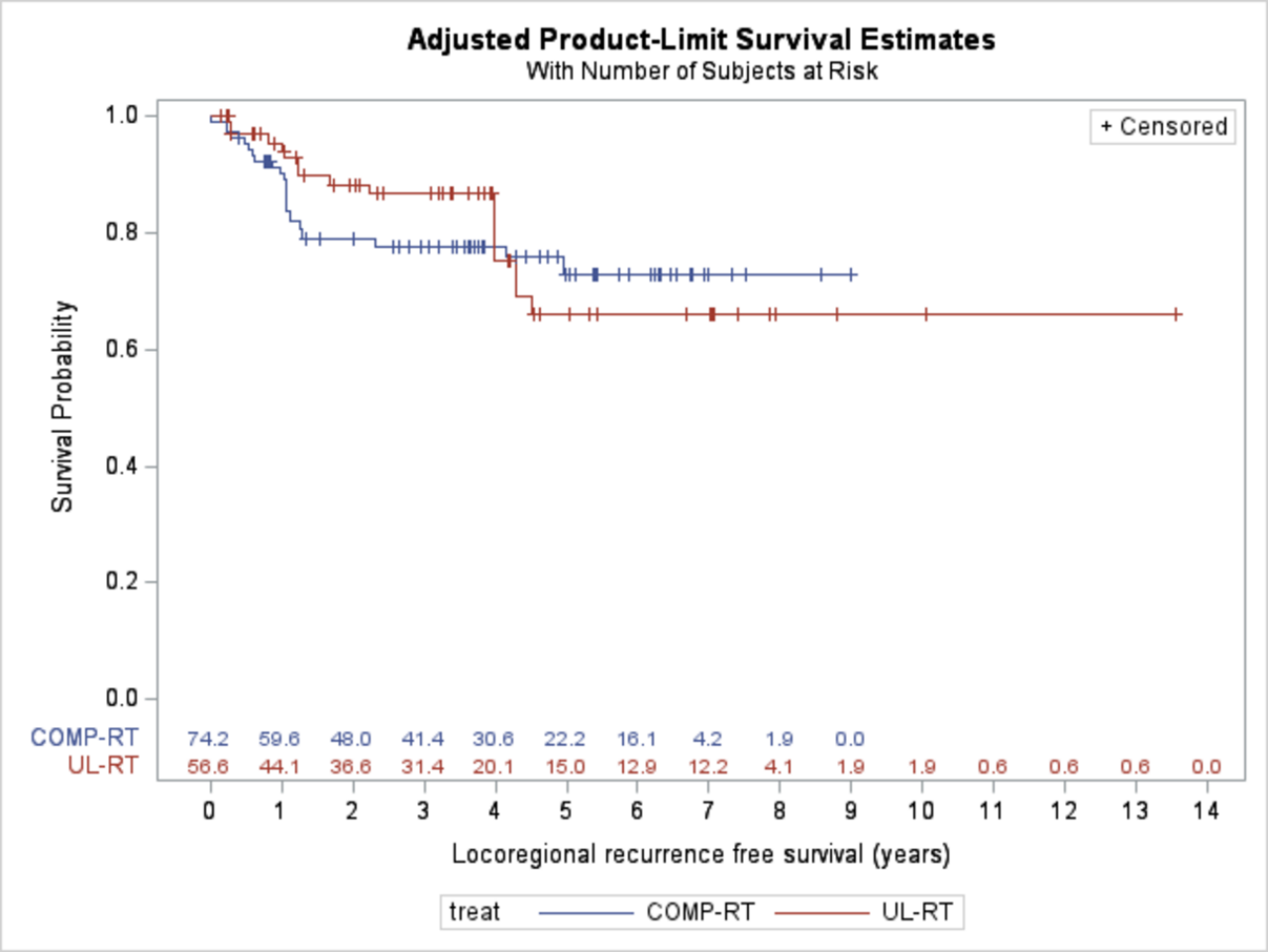
Figure 1. Overall survival curves with regard to irradiation volumes after propensity score matching
*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy

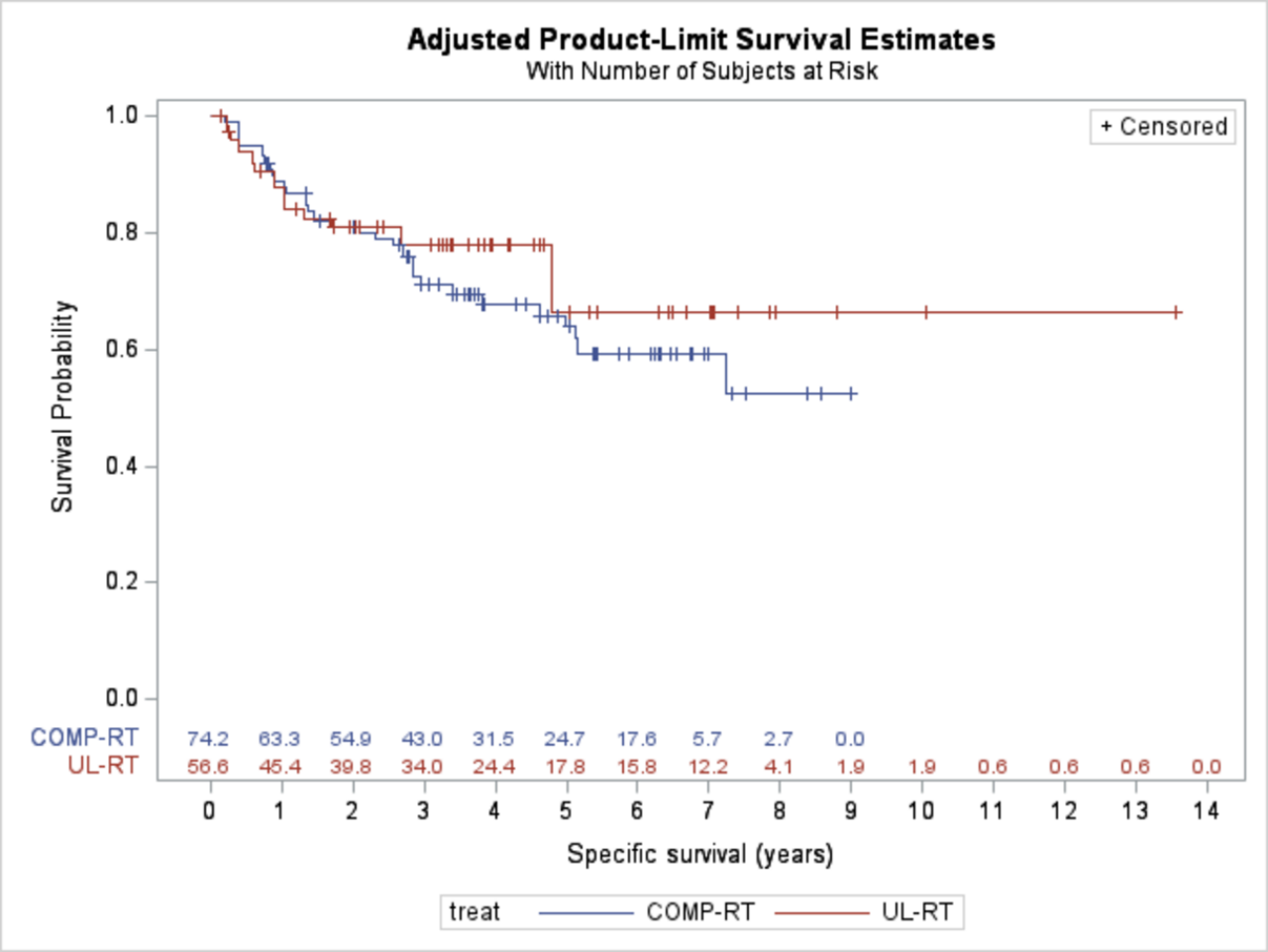
Figure 2. Locoregional recurrence free survival with regard to irradiation volumes after propensity score matching
*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy

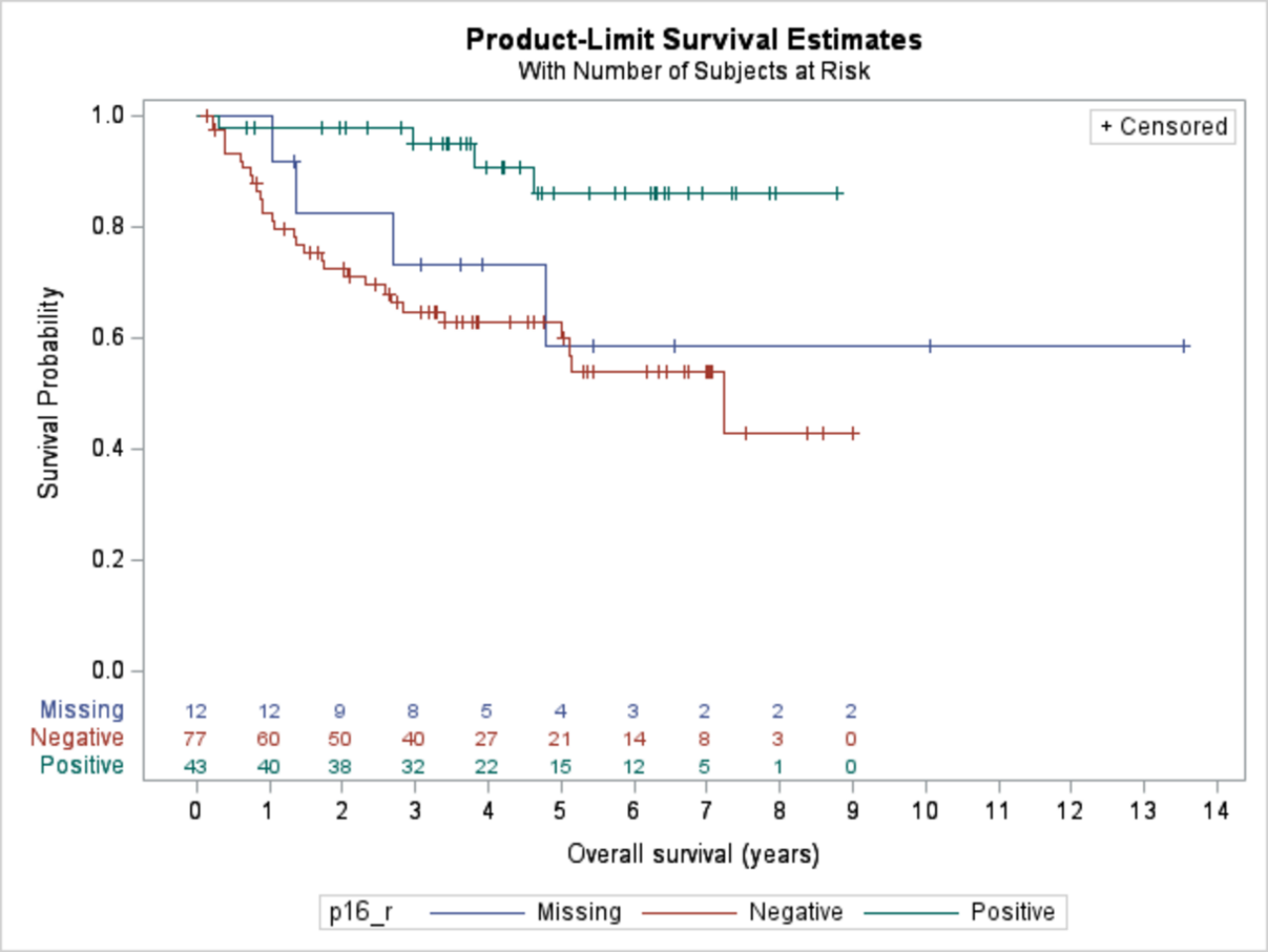
Figure 3. Specific survival curves with regard to irradiation volumes after propensity score matching
*UL-RT = unilateral radiotherapy ; **COMP-RT = comprehensive radiotherapy

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
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
COMP-RT 74.2 63.3 54.9 43.0 31.5 24.7 17.6 5.7 2.7 0.0
UL-RT 56.6 45.4 39.8 34.0 24.4 17.8 15.8 12.2 4.1 1.9 1.9 0.6 0.6 0.6 0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Overall survival (years)
treat COMP-RT UL-RT


Adjusted Product-Limit Survival Estimates
With Number of Subjects at Risk
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
COMP-RT 74.2 59.6 48.0 41.4 30.6 22.2 16.1 4.2 1.9 0.0
UL-RT 56.6 44.1 36.6 31.4 20.1 15.0 12.9 12.2 4.1 1.9 1.9 0.6 0.6 0.6 0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Locoregional recurrence free survival (years)
treat COMP-RT UL-RT


Adjusted Product-Limit Survival Estimates
With Number of Subjects at Risk
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
COMP-RT 74.2 63.3 54.9 43.0 31.5 24.7 17.6 5.7 2.7 0.0
UL-RT 56.6 45.4 39.8 34.0 24.4 17.8 15.8 12.2 4.1 1.9 1.9 0.6 0.6 0.6 0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Specific survival (years)
treat COMP-RT UL-RT


Product-Limit Survival Estimates
With Number of Subjects at Risk
+ Censored
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Missing 12 12 9 8 5 4 3 2 2 2
Negative 77 60 50 40 27 21 14 8 3 0
Positive 43 40 38 32 22 15 12 5 1 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Overall survival (years)
p16_r Missing Negative Positive