

**The use and variation of radiotherapy as primary treatment  
of cutaneous squamous cell carcinoma in the Netherlands in  
the period 2001-2015.**

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## **The use and variation of radiotherapy as primary treatment of cutaneous squamous cell carcinoma in the Netherlands in the period 2001-2015.**

### **Abstract:**

*Objective:* Aim of this study is to determine the use and variation in use of radiotherapy (RT), as the primary treatment of first primary diagnosed cutaneous squamous cell carcinoma (cSCC) in the Netherlands in the period 2001-2015 and to determine factors associated with the use of RT.

*Methods:* All patients newly diagnosed with cSCC in the period 2001-2015 were selected from the Netherlands Cancer Registry. Baseline characteristics were analyzed with a Chi-squared test, to explore whether the variables differ statistically significantly between treatment-groups. The distribution of tumor and patients characteristics were assessed between patients treated with and without RT. Logistic regression analyses were performed to identify factors associated with the use of RT.

*Results:* The total number of patients diagnosed with cSCC between 2001 and 2015 was 96406 and the average utilization rate of RT was 1.3% and varied between 2.3% and 0.7% over the years. The average utilization rate of RT for patients with an indication for RT following the Dutch guidelines in the period 2010-2015 was 7.2% and varied between 5.9% and 11.2%. Patients diagnosed with a clinical stage II, II of IV cSCC had a higher chance of receiving RT compared to patients with a stage I cSCC. The largest association was found for stage IV (OR=61.45, 95% CI=41.69-90.56). Compared to skin of the lip, RT was administered less often at the trunk (OR=0.72, 95% CI=0.53-0.97). Presence of an RT department in the hospital of first contact was also positively related with use of RT (OR=1.89, 95% CI=1.64-2.18). In the group of patients with an indication for RT (based on Dutch guidelines), presence of an RT department was also positively associated with use of RT (OR=1.57, 95% CI=1.09-2.26).

*Conclusion:* The use and variation in use of RT as primary treatment for cSCC was very limited for all patients. Utilization rate and variation in use of RT was higher for patients with an indication for RT. Tumors located on skin of the lip and on the trunk are most likely to be treated with RT, RT was administered more frequently when the patient had a higher clinical stage. The presence of a RT department in the hospital of diagnosis is positively associated with RT use. Further research is needed to assess whether RT has been appropriately used as a primary treatment for cSCC.

## Introduction

In the Netherlands, skin cancer is responsible for 52% of all cancers diagnosed [1]. Skin cancer is primarily divided into melanoma, the most aggressive form of skin cancer (10% of all skin cancers) and nonmelanoma skin malignancies (90% of all skin cancers). Nonmelanoma skin cancer can roughly be divided into cutaneous basal cell carcinoma (BCC, 75%) and cutaneous squamous cell carcinoma (cSCC, 25%) [1-2]. In contrast to cBCC, cSCC has a potential (of around 16%) to metastasize [3] and therefore therapy is important [4]. cSCC of the skin originates from DNA-damage of keratinocytes in the stratum germinative (stratum basale and stratum spinosum) of the epidermis [5]. cSCC initially appears as a skin-colored or light red nodule, often with a rough surface (hyperkeratosis), the nodule slowly enlarge overtime and can grow into a large tumor [6]. The main etiological factor for the development of cSCC is chronic exposure to UV light [7]. This is supported by the fact that 80% of the cSCC is located in the head and neck area and the remaining 20% mainly in the sun exposed parts of the trunk and extremities [1,8]. In addition, people with skin type I-II have an increased risk of developing cSCC [9]. cSCC is also more common in the elderly (75% of all diagnoses is in those aged > 65 years) and almost twice as often diagnosed in men than in women [1].

The annual incidence of cSCC is still increasing in the Netherlands while the incidence of almost all other malignancies has leveled off in recent years [1,10-13]. The incidence between 1989 and 2005 has increased with 2.3% per year [12]. The European age-standardized incidence rate (ESR) increased for men and women from 107.6 per 100,000 inhabitants in 1989 to 170.4 per 100,000 inhabitants in 2017 and from 68.7 per 100,000 inhabitants in 1989 to 92.6 per 100,000 inhabitants, respectively. The mean 10-year relative survival of cSCC is 90% [1]. The importance of evaluating and improving skin cancer policies and prevention campaigns in the Netherlands is widely recognized to halt the increasing trend of cSCC [1,11].

Treatment options for cSCC include surgery, radiotherapy (RT), chemotherapy, or any combination of these treatment modalities [14]. In general, surgical treatment is preferred because it allows for histological control of radicality [4,15]. However, primary RT offers a similar level of short- and long-term local control in cSCC, compared to surgery and may be preferred in a specific subset of patients [16-18]. Tumors on the lip, vestibulum nasi, ala, nasal tip and concha have RT as the preferred treatment. Advantages of RT are anatomy preservation, noninvasive outpatient treatment and no need for anesthesia [19]. Late side effects of RT as primary treatment, such as fibrosis or necrosis, are minimized by higher fractionation of RT [20]. Dutch guidelines about treatment for cSCC were first published in 2010 [6], and indicated which patients may benefit from RT. Based on Dutch guidelines, RT is preferred in tumors located on the lip (T2 tumors), the vestibulum nasi, sometimes the ala, nose tip and the concha [6,21,22]. Moreover, when discussing RT or surgery as the best treatment

for cSCC, a multidisciplinary team meeting (MDT) between a dermatologist, radiation oncologist and (plastic) surgeon is desired to determine the final treatment plan [4].

The multi-interpretability of Dutch guidelines about RT treatment for cSCC might lead to inconclusive use of RT. This may result in adverse consequences for the patient, unnecessary costs and regional or local variation in care [23]. The utilization rate of primary RT for cSCC is currently unknown in the Netherlands. However, in the United States, 42% of the patients with cSCC in the period 1988-2012 were treated with primary RT [24]. The use and variation in use of RT as primary treatment for cSCC, before and after the implementation of the Dutch RT guideline, has never been examined. Hence, the aim of this study is to determine the use and variation in use of RT, as the primary treatment of cSCC in the Netherlands for patients diagnosed with first cSCC in the period 2001-2015 and to determine factors associated with the use of RT

## **Method**

### *Patients*

All patients diagnosed with a first primary invasive cSCC between January 1<sup>st</sup> 2001 and December 31<sup>st</sup> 2015 were selected from the Netherlands Cancer Registry (NCR). The NCR includes information about diagnostics, patient and tumor characteristics and initial treatment of all patients diagnosed with cancer in the Netherlands [25]. Coding rules used for variables topography and morphology are in accordance with the International Classification of Diseases for Oncology (ICD-O) [26-27]. The following topography codes are included in the current study: C440(skin of the lip), C441(skin of the eyelid), C442 (skin of the external ear) C443 (skin of unspecified parts of the face: cheek, chin, face, forehead, jaw, nose, temple), C444 (skin of the scalp and neck), C445 (skin of the trunk), C446 (skin of the upper limb and shoulder), C447 (skin of the lower limb and hip), C449 (skin, not otherwise specified) and C632 (skin of the scrotum).

### *Analyses*

Baseline characteristics were analyzed with a Chi-squared test, to explore whether the variables differ statistically significantly between the group of patients that received primary RT and the group of patients who did not receive primary RT (RT vs. No-RT). The patients with cSCC who had (neo)adjuvant RT were assigned to the No-RT group because their primary treatment was not RT. The variables analyzed were: sex, age at time of diagnosis, topography, grade, morphology, whether there was an indication for RT (RTindication), whether a RT facility was available in the hospital of first contact (RTinHouse) and clinical stage. The stage of the tumor is based on the TNM system of the Union for International Cancer Control (UICC) [28]. In case the clinical stage was unknown, the pathological stage was used.

Age was categorized as follow: 0-44, 45-69, 70-79 and 80 years and older. Topography locations C63.2, C44.1, C44.6, C44.7 and C44.9 are grouped together in "other" because the numbers of tumors in these locations were low. Morphology was categorized as: the codes 8010, 8051, 8072, 8073, 8074, 8075, 8076, 8070, 8083 and 8084 are grouped under "other". The variable RT Indication (yes or no) was created to determine whether the patient had an indication for RT based on Dutch guidelines. RT Indication was defined as T2 tumors located on the lip, the vestibulum nasi, the ala, nose tip and the concha (ICD-O codes: C44.0, C44.2 and C44.3) [6,27] . The variable RTinHouse (yes or no) distinguish hospitals of first contact with and without an own RT department.

The use of RT was analyzed for all patients and for patients who had an indication for RT (indication group). Also the distribution of clinical stage, topography and RTinHouse between all patients and patients with primary RT was assessed. These analyses were stratified by RT Indication for variables topography and RTinHouse. Finally, a logistic regression analysis was performed to assess factors statistically significantly associated with RT use for all patients and for patients in the RT indication group specifically. Initially a univariable regression analysis was performed and variables significantly associated with RT use in univariable analysis were included in a multivariable regression model. Results were presented as odds ratio's (OR) and 95%-Confidence Interval (95% CI). All analyses were performed in STATA (version 16.1), the critical P-value was set to <0.05 in all of the tests.

## Results

### *RT use and patients characteristics*

In total 96,406 patients were diagnosed with a primary cSCC between 2001 and 2015 and 1.2% were treated with primary RT (Table 1). The utilization rate of RT decreased from 2.3% in 2001 to 0.8% in 2015. A difference in use of RT between men and women was observed, as 1.2% of all men and 0.9% of all women were irradiated. In general, the use of RT was associated with a higher mean age (75.8 years) compared with those who received other primary treatment (74.5 years). Skin of the trunk was the most commonly irradiated location (2.7%), followed by skin of the lip (2.6%) and external ear (2.2%). More than 8% of all patients with an indication for RT (from 2010 included in Dutch guidelines) were treated with RT. Patients diagnosed with clinical stage III and IV cSCC were treated with RT in 15.8% and 26.4% of the cases, respectively. If there was a RT-department in the hospital of first contact, 2.1% of the cSCC patients was treated with RT compared to 0.9% when no RT-department was in the hospital. No relevant differences were found for the other variables. All the analyzed variables were found to be statistically significantly associated with treatment ( $P$ -value $<0.05$ ), except for the variable morphology.

### *Use of RT over time in the indication group*

In the indication group ( $N=2,114$ ), the utilization rate of RT decreased from 17.2% in 2001, which was the study year with highest use rate of RT, to 6.2% in 2015 (figure 1). For all years, relative RT use was higher in the indication group than in all patients. Little variation in RT use was observed over time in all patients, it varied between 2.3% and 0.7%. However, the use of RT over time showed a large variation (17.2%-5.8%) for patients who had an indication for RT (figure 1). For patients in the indication group a large decrease in RT use (11%) over the years 2001-2004 could be observed. In the period 2010-2015, there was an average use of RT of 7.2% for patients with an indication of RT. The average use of RT for these patients in the period 2001-2009 was 10.5%.

### *Distribution of factors between treatment-groups*

The distribution of clinical stage in all patients, stratified for those receiving RT and no-RT (figure 2), showed that the proportion of patients with stage II, III and IV was higher in the RT group compared to the No-RT group. Clinical stage was often unknown, in the RT group 12% had an unknown clinical stage and in the No-RT group 10% was unknown. So, only patients with a known clinical stage were included for the distribution of clinical stage. The RT group consisted of an 22 times higher proportion (11%) of stage III than the No-RT group (0.5%), in addition, the proportion of stage II and IV were respectively six and ten times higher in the RT group. The distribution of clinical stage (figure 2) was not shown for indication group because it

only includes stadium II. In figure 3, the distribution of locations were shown. The proportion of all patients with a tumor located on the trunk was larger in the RT group (20%) compared to the No-RT group (8%). For tumors located on skin of the lip, a larger proportion in RT group (6%) compared to No-RT group (3%) was also seen. The RT-group, furthermore, consisted of a two times higher proportion (20%) of patients with a tumor located on the external ear than the No-RT group (10%). In the indication group, a higher proportion of patients with tumor on the skin of the lip and external ear was present. Figure 4 described the distribution of variable RTinHouse, the presence of an own RT-department had a larger share in the RT-group (32%) compared to the No-RT group (17%) for all patients. In the indication group, the presence of an own RT-department had also a larger share in the RT-group (30%) compared to the No-RT group (22%).

### *Multivariable regression analysis*

Table 2 demonstrates the results of univariable and multivariable logistic regression analyses for all patients and specifically for patients with an indication for RT.

For all patients, a higher stage was associated with more frequent use of RT and clinical stage IV was most often associated with RT use (OR=61.45, 95% CI=41.69-90.56) (Table 2).

Furthermore, a tumor with differentiation grade 2 (OR=1.37, 95% CI=1.12-1.65) had a positive association with RT-use as well, compared to tumor with grade 1. RT was administered more often in patients with a tumor on the lip, followed by trunk (OR=0.72, 95% CI=0.53-0.97) and external ear (OR=0.54, 95% CI=0.40-0.74). Finally, presence of an RT department in the hospital of first contact was also positively related with use of RT (OR=1.89, 95% CI=1.64-2.18). Morphology for all patients was not statistically significant in univariable regression analysis.

In the indication group, RT was administered more often in patients with a tumor located on skin of the lip, followed by external ear (OR=0.50, 95% CI=0.27-0.94) and parts of the face (OR=0.27, 95% CI=0.15-0.48). Also for patients in the indication group, the presence of an RT department in the hospital of first contact (OR=1.57, 95% CI=1.09-2.26) was positively related with use of RT. Age, gender and morphology were not statistically significant in univariable regression analysis for patients with an indication for RT and therefore were not included in multivariable analysis.

Table 1. Patient, tumor and treatment characteristics. (N=96406)

	Radiotherapy(N=1068)		No-Radiotherapy(N=95338)		P-value
	N	%	N	%	
<b>Incidence Year</b>					
2001	78	2.3	3377	97.7	<0.01
2002	68	1.9	3421	98.1	
2003	69	1.9	3643	98.1	
2004	56	1.3	4118	98.7	
2005	69	1.5	4628	98.5	
2006	70	1.4	5080	98.6	
2007	74	1.3	5641	98.7	
2008	69	1.1	6141	98.9	
2009	66	0.9	6713	99.1	
2010	70	0.8	7784	99.2	
2011	65	0.7	8779	99.3	
2012	85	0.9	8858	99.1	
2013	63	0.7	9128	99.3	
2014	93	1.0	9221	99.0	
2015	73	0.8	8806	99.2	
<b>Gender</b>					
men	696	1.2	53918	98.8	<0.01
women	372	0.9	41420	99.1	
<b>Age</b>					
Mean age	75.8		74.5		
0-44	20	1.6	1270	98.4	<0.01
45-69	269	0.9	27323	99.1	
70-79	275	0.9	31721	99.1	
≥80	504	1.4	35024	98.6	
<b>Topography</b>					
Lip	64	2.6	2396	97.4	<0.01
External Ear	210	2.2	9538	97.8	
Parts of Face	301	0.8	37627	99.2	
Scalp and Neck	174	1.4	12024	98.6	
Trunk	216	2.7	7768	97.3	
Other	103	0.4	25985	99.6	
<b>Differentiaton Grade</b>					
1	163	0.5	33775	99.5	<0.01
2	256	1.0	25016	99.0	
3	84	1.5	5510	98.5	
Unknown	565	1.8	31037	98.2	
<b>Morphology</b>					
8070	891	1.1	79421	98.9	0.23
8071	114	1.0	11190	90.0	
Other	63	1.3	4727	98.7	



Table 1 continued.

<b>RT-Indication</b>			
Yes	174 8.2	1940 91.8	<0.01
No	894 3.7	93398 96.3	
<b>Clinical Stage</b>			
I	395 0.5	79336 99.5	<0.01
II	403 6.1	6252 93.9	
III	100 15.8	534 84.2	
IV	44 26.4	123 73.6	
Unknown	126 1.4	9093 98.6	
<b>cT</b>			
1	405 0.7	62044 99.3	<0.01
2	386 7.2	4959 92.8	
3	82 19.1	347 80.9	
4	61 28.5	153 71.5	
Unknown	130 0.5	27615 99.5	
<b>cN</b>			
0	800 1.8	44529 98.2	<0.01
1	49 20.0	196 80.0	
2	19 27.9	49 72.1	
3	2 20.0	8 80.0	
Unknown	198 0.4	50556 99.6	
<b>cM</b>			
0	889 1.2	70792 98.8	<0.01
1	9 16.4	46 83.6	
Unknown	170 0.7	24500 99.3	
<b>RTinHouse</b>			
Yes	340 2.1	16103 97.9	<0.01
No	728 0.9	79235 99.1	

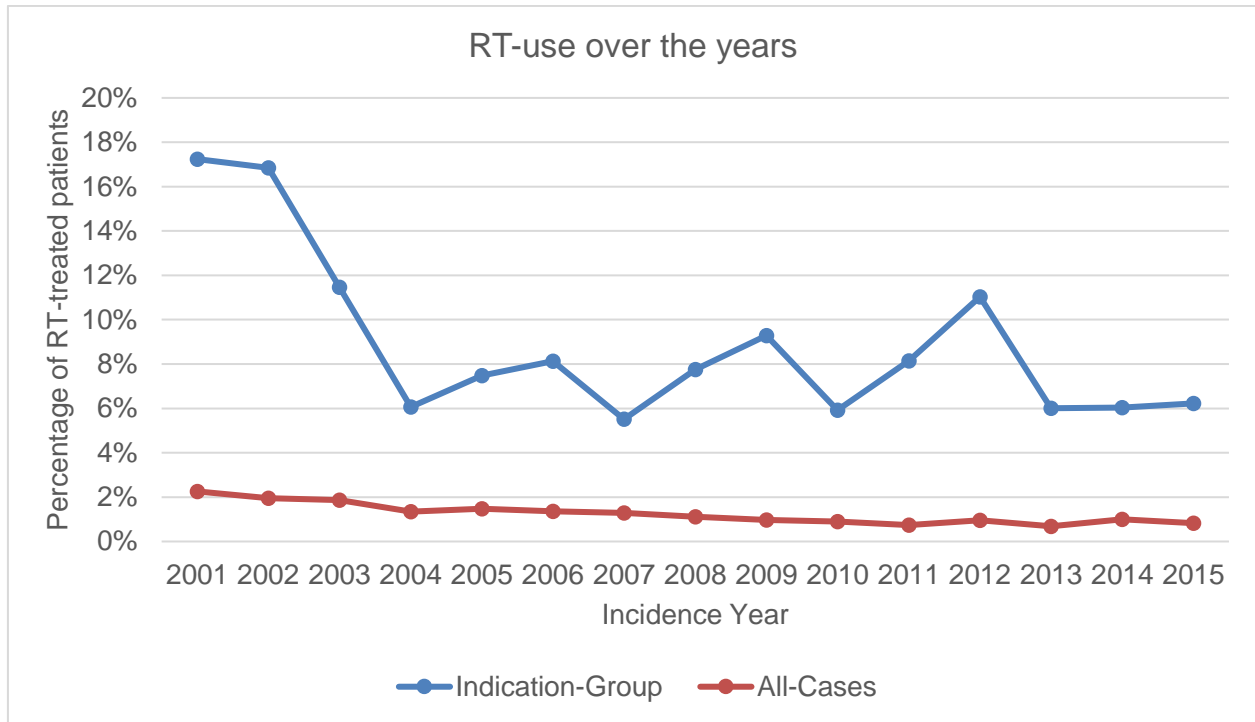


Figure 1. Use of RT over time, stratified for all patients diagnosed with cSCC and patients with an indication for RT (indication group).

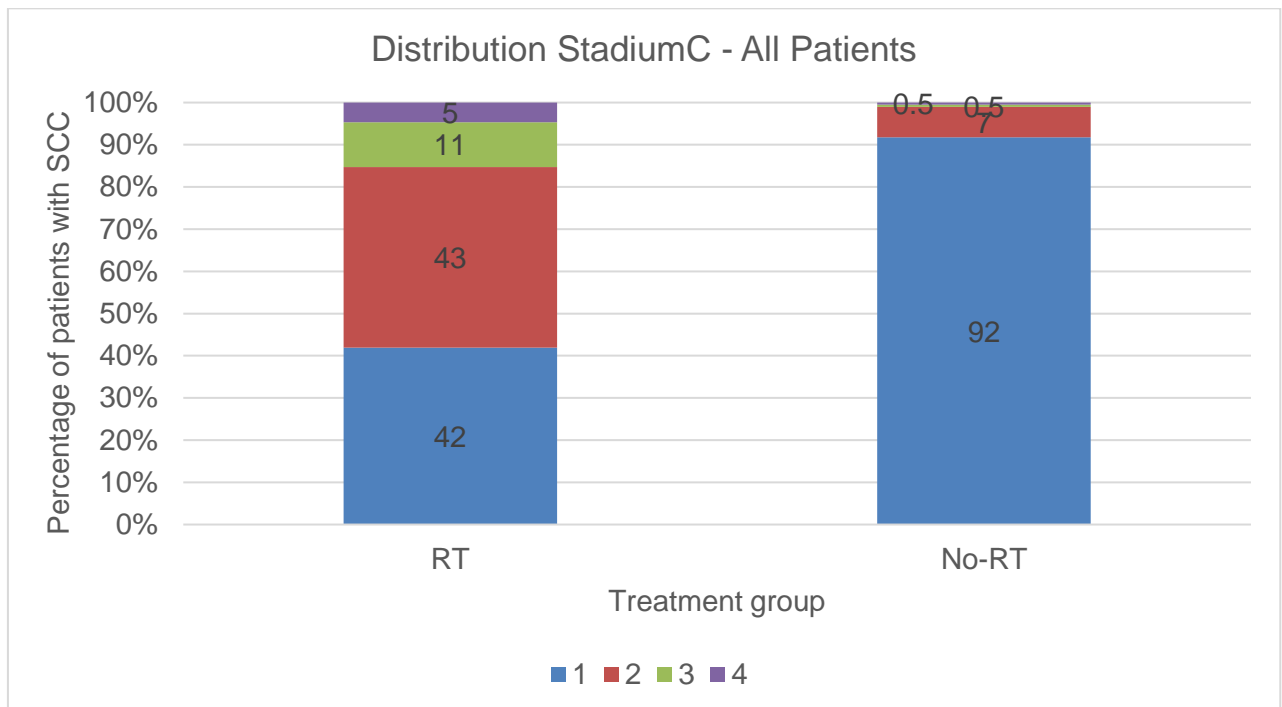


Figure 2. Distribution of Clinical Stage in the RT- group and No-RT group for all patients.

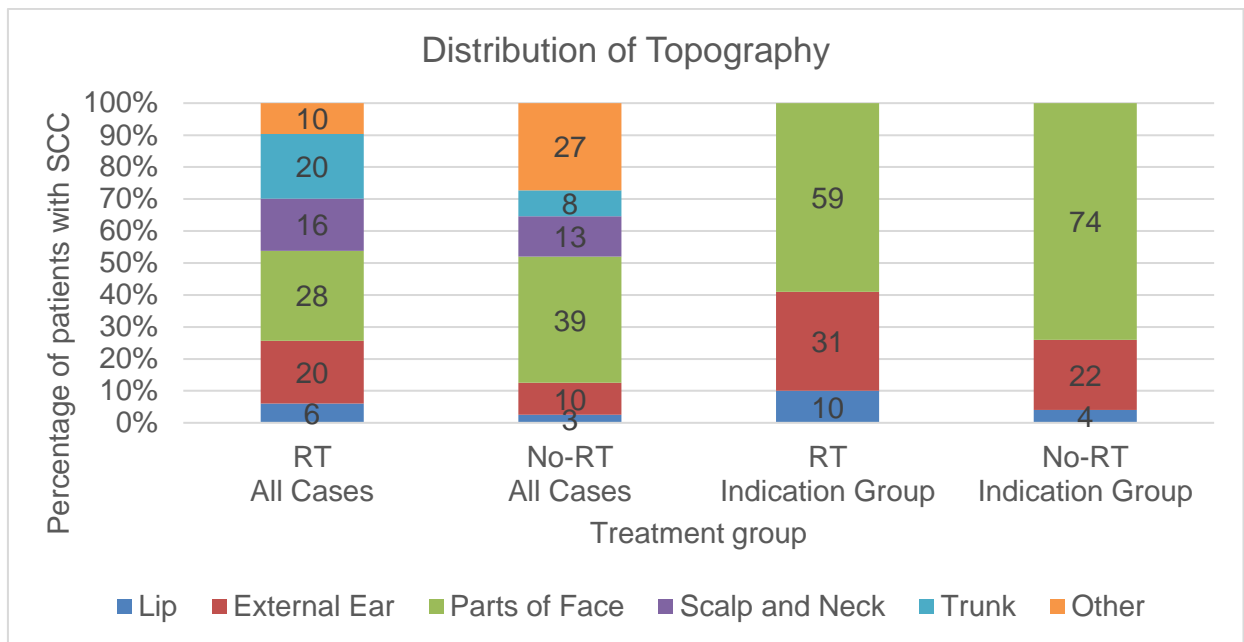


Figure 3. Distribution of tumor location, in the RT-group and No-RT group, stratified for all patients diagnosed with cSCC and patients with an indication for RT (indication group).

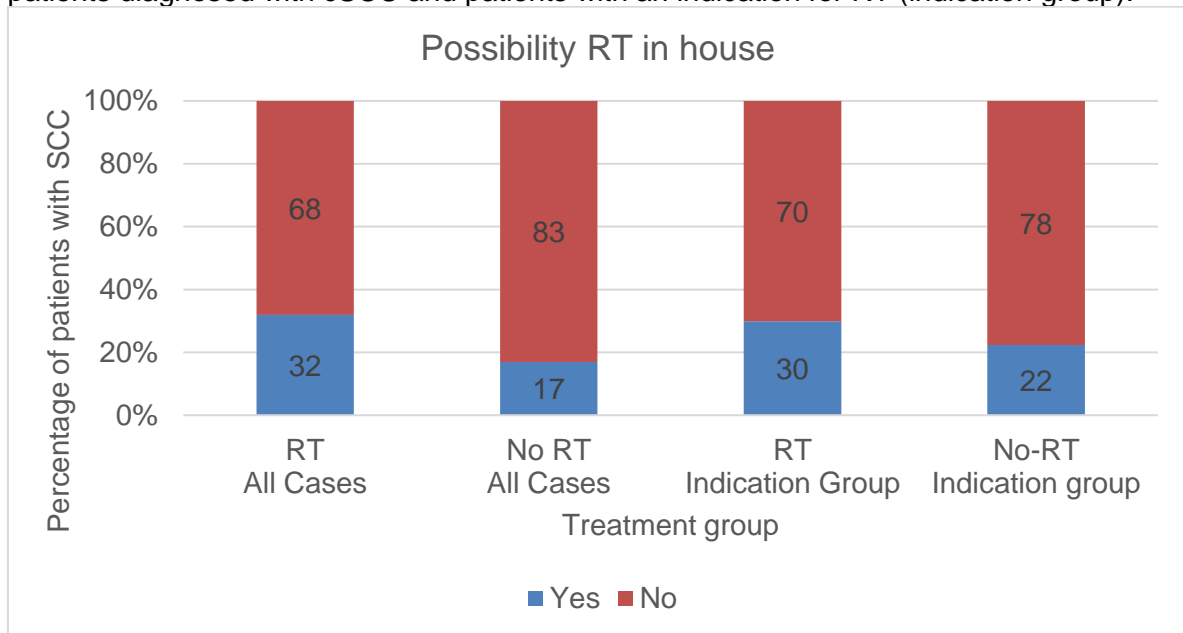


Figure 4. Distribution of the presence of a RT-department in hospital of first contact in the RT-group and No-RT group, stratified for all patients diagnosed with cSCC and patients with an indication for RT (indication group).

Table 2. Univariable and multivariable logistic

	All Patients - Univariable			All Patients - Multivariable			Indication Group -Univariable			Indication Group -Multivariable		
	OR	P-value	95% CI	OR	95% CI		OR	P-value	95% CI	OR	95% CI	
<b>Gender</b>	0.70	<0.01	0.61 0.79	1.00			0.92	0.63	0.66 1.28			
<i>Man</i>				1.00								
<i>Woman</i>				0.92	0.80 1.06							
<b>Age(years)</b>	1.17	0.01	1.03 1.32	1.00			0.79	0.18	0.56 1.11			
0-44				1.00								
45-70				0.78	0.46 1.20							
70-79				0.75	0.52 1.35							
≥80				1.07	0.75 2.54							
<b>Clinical Stage</b>	0.93	<0.01	0.92 0.95	1.00			-					
I				1.00								
II				13.44	11.93 15.62							
III				33.11	25.76 42.57							
IV				61.45	41.69 90.56							
Unknown				2.62	2.13 3.21							
<b>Differentiation Grade</b>	1.13	<0.01	1.11 1.15	1.00			1.23	<0.01	1.17 1.28			
1				1.00						1.00		
2				1.37	1.12 1.65					1.46	0.83 2.57	
3				1.31	0.98 1.71					1.38	0.69 2.75	
Unknown				3.42	2.85 4.09					5.30	3.15 8.93	
<b>Topography</b>	0.998	<0.01	0.997 0.998	1.00			0.65	<0.01	0.55 0.77			
Lip				1.00						1.00		
External Ear				0.54	0.40 0.74					0.50	0.27 0.94	
Parts of Face				0.25	0.19 0.34					0.27	0.15 0.48	
Scalp and Neck				0.31	0.23 0.42							
Trunk				0.72	0.53 0.97							
Other				0.11	0.09 0.17							
<b>RTinHouse</b>	2.30	<0.01	2.02 2.62	1.00			1.48	0.03	1.05 2.08			
No				1.00						1.00		
Yes				1.89	1.64 2.18					1.57	1.09 2.26	

## Discussion

The aim of this study was to determine the use and variation in use of RT over time, as part of the primary treatment of cSCC in the Netherlands in the period 2001-2015 and to determine factors associated with RT-use. First of all, all patient and tumor characteristics investigated, differ statistically significantly between patients receiving RT or not, except for morphology. The use of RT turns out to be very limited and vary between 2.3% and 0.7% over the years. As expected, RT is more frequently used in the RT indication group compared to the general population. After the implementation of treatment guidelines in 2010, the recommendation of the Dutch guidelines about cSCC treatment was followed in only 7.2% of the patients compared to 10.5% before the introduction of the guideline. Distribution of different variables over treatment-groups showed differences between the groups. Multivariable logistic regression demonstrated that topographic location (skin of the lip and skin of the trunk), clinical stage (stage III and IV) and the presence of an own RT department in the hospital of first contact are statistically significantly associated with the use of RT.

The average utilization of RT in the patients with an indication of RT implied a limited use because of not all the patients with an indication, following the guidelines, received RT as primary treatment. But, the guidelines on RT as a treatment for cSCC have included ambiguous advice: discussion in a MDT or tumors with preference for RT. The aim of treatment guidelines is to uniformize healthcare, contributing to the right decision about appropriate healthcare and making evidence-based decisions [29-30]. The known scientific evidence for the treatment of cSCC did not include a single option as the best treatment for cSCC. Also seen in the guidelines, different treatments had overlapping preferred tumors to treat [4]. Explanation for the limited use of RT, could be the multi-interpretable formulation of guidelines, no proper compliance with guidelines or lack of evidence for appropriate treatment..

Another reason for limited use of RT could be the outcome of an MDT, in which is decided that surgery is the best treatment and hence, there is still compliance to the RT guideline. MDTs are an integrated team approach to planning treatment and care for individual patients, and are a common care paradigm used in oncology [31]. Different studies emphasize the importance of an MDT especially in non-melanoma cancer [32-33]. Information included in this study from the NCR, did not have any details about the presence of a MDT, the discussion contained in the MDT, or the recommendation that followed from the MDT. While the rationale for preferred treatment which is discussed in a MDT, is important for assessing the effective use of RT.

In addition, another important reason for the limited use of RT could be the choices made by patients themselves, patients may also prefer surgery over RT. The preference for surgery may have been caused by the rise of Mohs surgery, this treatment has the highest cure rates and conserves the maximum amount of normal tissue [34]. Based on Dutch guidelines

about treatment of cSCC, Mohs surgery can be considered for clinical stage I and II in locations where tissue sparing is desired, i.e. in the face [4]. Tumor characteristics (Table 1) showed most of the tumors had clinical stage I and locations on the face. Patients maybe has preferred Mohs surgery over RT. A study who investigated influence of patients factor on choice of treatment, founds that performance status, age and anatomical site were significant factors for choosing RT [35]. The patient population of this study is very diverse in age but also in topographical locations of tumors, this study did not included performance status. Diversity of these variables could explain the low use of RT, patients did not prefer RT.

Multivariable regression analysis in this study implies several factors that are positively related with RT-use. Tumors located on the skin of the lip have the highest probability to be treated with RT followed by the trunk and external ear. Tumors located on the lip are advised to be treated with RT by Dutch guidelines, same goes for location on external ear. Interestingly, the trunk is not included as a recommended location in the guidelines regarding RT. The positive relation between RT use and tumor located on the trunk can not be explained by literature but perhaps information of an MDT or patients choice were decisive.

Another positive relation is found between RT use and higher stage tumors. Patients with a stage IV tumor have more chance to receive RT (OR=61.45), compared to patients with a stage I tumor. The high OR indicates how important clinical stage is in choosing RT as primary treatment or not. An advantage of RT is anatomy preservation, which is an additional advantage when the tumor is very large and surgery has a major impact [19]. Anatomy preservation is preferred in cases where a bigger wound appeared, which could declare the positive relation between RT use and higher stages. Another advantage of RT is that elderly and co-morbid patients with poor performance status can benefit from RT where surgery is no option [36]. In the elderly fibroblasts and collagen synthesis is reduced, wound healing and epithelialization are slower with this generation [37-38]. In combination with the higher and increasing mean age of the cSCC patients in the Netherlands [1], use of RT in larger tumors is also preferred.

The last positive relation was found between RT use and the presence of an own RT-department in hospital of first contact. This implies that if the hospital of first diagnosis had its own RT-department, this patient is more likely to be treated with RT than if it does not have an own RT-department. Maybe because of the lack of an own RT department means referral to a nearby hospital and therefore more time and money has to be invested in and/or by a patient. And also travel time can be a declaring reason for this fact, known is that travel time influence the choice of hospital [39]. So, if the hospital of first contact did not have an own RT department the patient has referred to a nearby hospital. Travel time in the Netherlands is not such a large amount but apparently has an influence on the choice RT as treatment, not every hospital in the Netherlands had their own RT department.

### *Strengths and limitations*

The strength of this study is that it is a nationwide population-based study. Also a strength of this study is to monitor use of guidelines and determine RT use as primary treatment for cSCC, which have never been studied in the Netherlands before. A major limitation of this study is the lack of information on treatments applied in recent years. The NCR did not register all information about treatment details of cSCC after the year 2015, because new diagnoses have been automatically imported since ten. Furthermore, discussions which have been taken place in a MDT could not be evaluated as this information also lacked in the NCR. A recommendation for subsequent research could be that the content of MDTs be studied to better understand treatment decision in patients with cSCC and to expose factors precisely which are associated with RT use. This subsequent research can contribute to determine the correct use of RT. Another weakness is that the indication group could not be defined specific enough, the nose did not have an own topographical location. Topographical location C44.3 includes all unspecified parts of the face and not just only the nose as mentioned in the guideline. Location C44.3 is nevertheless included as representation of the nose, based on expert advice. In addition, the number of RT-treated patients is also too low to determine variation between regions or institutes.

### **Conclusion**

The aim of this study was to determine the use and variation in use of RT, as the primary treatment of cSCC in the Netherlands in the period 2001-2015 and to determine factors associated with the use of RT. The use of RT in general population was very limited and varied between 2.3% and 0.7% over the years 2001-2015. As expected, higher use of RT was seen in indication group where the use varied between 17,3% and 6.1%. Tumors located on skin of the lip and on the trunk are most likely to be treated with RT, the chance of RT as treatment becomes higher when the patient has a higher clinical stage cSCC and RT is used more when hospital of first contact has an own RT department. The main practical implications of this study relate to determining use of RT as the primary treatment of cSCC and showed associations between different variables and use of RT. Further research is needed to assess whether RT has been appropriately used as a primary treatment for cSCC.

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