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Review Article

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Radiotherapy for Tracheal Squamous Cell Carcinoma: A Review

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Abstract

Tracheal cancer is a rare localization without official recommendation nether European nor French. This review summarizes the data published about tracheal squamous cell carcinoma treated with radiotherapy in terms of dose and fractionation, techniques, volume, toxicity, overall survival and local control.

Keywords: Tracheal Cancer; Radiotherapy; Squamous Cell Carcinoma

Introduction

Tracheal cancers are a rare primary tumour location, estimated at less than 0.1 cases per 100,000 inhabitants [1]. No staging classification exists specifically dedicated to tracheal tumours. Clinically, initial symptoms such as haemoptysis, dyspnea, cough, or even stridor are encountered and guide the initial assessment [2,3]. Due to the low incidence, there is neither French nor European recommendation for management of these tumours. Several histological varieties are described: squamous cell carcinomas, adenocarcinomas as well as adenoid cystic carcinomas. The history and age at diagnosis are different amongst these histologies. Smoking, male predominance and rapid progression are associated with tracheal squamous cell carcinoma. A contrario, the male to female ratio is similar, with little or no history of smoking and slow progression in case of adenoid cystic carcinoma [3]. Squamous cell carcinomas are reputed to be more radiosensitive and more lymphophilic than adenoid cystic carcinomas. Thus, the doses and fractionations, margins and volumes recommended in radiotherapy are different according to the histologies, as realised for lung and head and neck cancers [4–6]. In case of tracheal cancer, there is no consensus dedicated to radiation therapy. Tracheal cancer treatment can use endoscopic resection if limited lesion, surgery – realised in first intention, radiotherapy and systemic treatment [3]. Several elements may contraindicate surgery, in particular if impossibility of adequate margin or extension to adjacent organs or metastatic disease. Radiotherapy can be done as an adjuvant treatment as well as an exclusive treatment, associated or not with systemic treatment. This review summarizes the main elements published about squamous cell carcinoma of the trachea treated with radiotherapy, in terms of modalities, therapeutic regimens, local control and survival, acute and late side effects

Material and Methods

A review of the literature was made on the pubmed database in French and English from 2012 to April 2022 over the last ten years, due to the change in radiotherapy techniques, in particular use of intensity modulation techniques, reference in lung and head and neck cancers. Series with only brachytherapy have been excluded due the high level of specialization necessary for this technique.

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Larnaudie A et al., Arch Clin Med Case Rep 2022
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- The series and case reports were selected if inclusion of squamous cell carcinoma of the trachea with radiotherapy treatment. The MESH words used were "tracheal cancer"; "squamous cell carcinoma" and "radiotherapy", "radiation therapy"
- From 2012 to 2022: 125 articles were found, 18 were selected based on title and abstract, 17 were selected after reading the full text.

For comparison, the largest series or case reports detailing the radiotherapy treatment performed, published before 2012 were selected.

Results

Several publications have studied radiotherapy in tracheal cancers, the 17 articles selected include 9 case reports and 8 retrospective series published after 2012. Squamous cell carcinomas accounted for more than half of the histologies. Table 1 summarizes the data found in terms of treatment, toxicity and prognostic. Concerning indications and systemic treatment modalities, surgery was the first treatment, exclusive radiotherapy being performed only in case of surgical or anaesthetic contraindication or patient refusal. Systemic treatments were realised as neoadjuvant or concomitant with radiotherapy. Almost all the studies found after 2012 used a platinum salt derivative, in the form of cisplatin. Cisplatin was delivered either at a dose of 100 mg/m^2 every three weeks or at a dose of 40 mg/m^2 weekly and/or in combination with other molecule. Only one serie include brachytherapy in the radiotherapy treatment [7]. Regarding radiotherapy, the techniques included 3D and IMRT in most of the cases, in photon. The dose varied between 64 and 70 Gy using an equivalent of 2 Gy by fraction (EQD2). Some series detailed volumes of radiotherapy. More specifically, 2 studies detailed the macroscopic volume of the GTV-P tumour based on imaging and endoscopy as well as the margins for the CTV without help of PET [8,9]. The CTV-P clinical volume was made with a margin of 3-5 cm craniocaudally and 1-2 cm

Table 1: Summary of series and case reports on squamous cell carcinoma of the trachea.

Series	N Characteristics	Treatment Dose and Volume	Toxicity	Local control and Survival
Series published after 2012				
Zeng and al 2021 Retrospective 1996-2016 [10]	32 patients M 72% / F 29% SCC 56% ACC 31% Surgery 50% Adjuvant RT 41% Definitive RT 56 % Induction CT 6%	**Technique** 3DRT 37% IMRT 34 % 2DRT 28% **Dose (1.8-2Gy)** 50-54 Gy with boost if R1 ou R2 60-70 Gy	**Late** No toxicity ≥ grade 3	At 5 year : OS 47% SSPLR 68% - better if surgery (93 % vs 46%,) DFS better if at least 68 Gy 68 Gy (44.4% vs 13.0%,)
Jiang and al 2020 Retrospective 2009-2019 [16]	49 patients M 55%/ F46% SCC 41 % ACC 21% Surgery 23% Definitive RT 26 %	ND	ND	At 5 year OS 14% SCC OS 8% ACC OS 29%
Yusuf and al 2019 Retrospective 2004-2014 [17]	300 patients M 56%/ F 44% SCC 43% ACC 33% CT 23% Adjuvant RT	**Dose** RT dose superior to 30 Gy	ND	At 5 year OS SCC 33% ACC 98%
Hararah and al 2019 Database NCD 2004-2012 [14]	532 patients M 64%/ F36 % Surgery 40% Definitive RT with CT 26 % ; RT alone 17%	**Dose** ≥60 Gy for 45% of the patients	ND	At 5 year 0S 25% Similar in case of surgery and adjuvant treatment versus radiochemotherapy Prognostic factor : age ≥65 years, ≥1 comorbidities, and palliative treatment
Agrawal and al 2017 Database SEER 1973-2011 [15]	1144 patients 327 Surgery M 47%/ F 53% ACC 28% SCC 40% Surgery Ajuvant RT (nd) Definitive RT (nd)	**ND**	ND	At 5 year OS 25% in 1973 and 30% in 2006 OS higher if surgery No difference RT alone versus no treatement

Larnaudie A et al., Arch Clin Med Case Rep 2022
DOI:10.26502/acmcr.96550539

Xie and al 2012 Retrospective 1988-2007 [7]	78 patients RT M 58%/ F 42% SCC 42 % ACC 15% Surgery 61 % Adjuvant RT 61 % Exclusive RT 38 % 78 patients : no RT (control)	ND	ND	At 5 year (RT) OS 42% LC 50% At 5 year (no RT) OS 28% LC 37%
Napieralska and al 2016 Retrospective [9]	48 patients SCC 64 % ACC 16% Adjuvant RT Exclusive RT Brachytherapy 17 CT 29 % Cisplatin alone or in combination with adriamycin, navelbine, etoposide, mitomycin C or 5-fluorouracil. 1-6 cycle	**Technique** RT3D IMRT Tomotherapy Brachytherapy (HDR) Iridium-192 **Dose** ***palliative RT (2-8Gy)*** in 2 to 16 fractions of 2 to 8 Gy ***Exclusive RT (1.6-3Gy)*** 42.5 - 82.6 Gy2 (median 66). Boost 10 - 12 Gy , A***djuvant RT*** 42.5 Gy	ND	At 12.7 months DFS : 14.5 % At 5 year SCC OS: 8% ACC OS 78% OS Prognostic factors : radiotherapy, PS, haemoptysis
Li and al 2013 Retrospective [22]	31 patients M 80 % / F20 % ACC 68% SCC 10% Surgery 97% Adjuvant RT 83% RT+CT 64%	**Dose** 60 Gy in 30 fractions	Emergent tracheotomy mediastinal emphysema and pneumothorax	At a median of 6 year (3-11 year) LC 77%
Cases reports published after 2012				
Hussein and al 2020 [23]	2 patients	**Dose** 60- 64 Gy	ND	ND
Al Asmar and al 2020 [24]	1 patient F SCC Induction CT Cisplatin docetaxel Then Radiochemotherapy	**ND**	ND	At the end of Radiochemotherapy partial response
Kovacs and al 2021 [12]	1 patient M Exclusive RT with concomitant CT Cisplatin 100 mg/m^2	**Dose (2.2Gy)** 60 Gy	Mucositis Tracheitis Anemia neutropenia Pneumonia	ND
Maller and al 2019 [21]	1 patient M SCC Adjuvant RT	ND	ND	Reccurent after 5 months Complete response after immunotherapy
Yathiraj and al 2017 [11]	1 patient M SCC Definitive RT with CT weekly cisplatin 40 mg/m2	**Technique** 3D **Dose (2Gy)** 60 Gy in 30 fractions	**Acute** Dermatitis grade 1 dysphagia grade 2 Loss of weight 9.5% **Late :** hypothyroidism	Complete response at 1 year
Tan and al 2016 [20]	1 patient M SCC After surgery of thyroid and radioiodine treatment Treatment with RT	**ND**	**ND**	ND
Imai and al 2016 [18]	1 patient SCC associated with HPV18	**ND**	**ND**	ND

Larnaudie A et al., Arch Clin Med Case Rep 2022
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Paliouras and al 2015 [25]	1 patient SCC associated with multiple papilloma Laser ablation then recurrence at 1 week adjuvant radiotherapy and chemotherapy CT Cisplatin 70 mg/m2	**Dose** 40 Gy in 20 fractions	**ND**	At 1 year : complete response
Luo and al 2014 [13]	1 patient M SCC With oesophageal SCC CT carboplatin etoposide	**Dose** 60 Gy in 30 fractions Sequential RT	Ventricular tachycardia	Complete response at 1 year
Series published before 2012 (selection)				
Urdaneta and al 2011 Database SEER [26] 1973-2004	578 patients M 56% / 44% SCC 45% ACC 16% Surgery 66% RT 61%	ND	ND	At 5 year, for localized disease OS 46% SCC OS 25 % ACC OS 90% Better OS if surgery No difference in adjuvant RT
Honings and al 2007 [27]	293 patients M 72% / F 29% SCC 53 % ACC 7% Surgery 12 % RT 53%	ND	ND	A 5 year OS 15%, OS if surgery 51%, Better prognostic with ACC
Case reports avant 2012 (selection)				
Videtic and al 2003 [28]	1 patient 2 induction cycle Exclusive RT avec Cisplatin	**Dose (2Gy)** 60 Gy in 30 fractions	ND	At 6 weeks and 2 year : complete response e A 3 year : lung and bones metastases
Haresh and al 2010 [29]	1 patient SCC Radiotherapy with carboplatin paclitaxel	**Dose** 60 Gy in 37 fractions	ND	A 2 year : complete response

Legend: SCC- Squamous Cell Carcinoma; ACC- Adenoid Cystic Carcinoma Carcinoma; ADK- Adenocarcinoma; F- Female; M- Male; RT- Radiotherapy; CT- Chemothérapie; OS- Overall Survival; DFS- Disease Free Survival; LRPFS- Locoregional Progression Free Surival; ND- Not Described; IMRT- Intensity Modulated Radiation Therapy

Table 2: Synthesis proposal on tracheal squamous cell carcinoma radiotherapy.

Treatment	Modalities	Possible indication
Induction Chemotherapy	Cisplatin associated with another molecule	In case of symptoms 1 retrospective serie
Concomitant Chemotherapy	Cisplatin 100 mg/m^2 Cisplatin 40 mg/m^2 Cisplatin associated with another molecule Rare : Carboplatin Paclitaxel	In case of incomplete resection or no surgery
Definitive Radiotherapy	Dose : 60-70 Gy in 2 Gy fraction Volumes GTV P : tumour correlated to endoscopic description and CT/ PET-CT exams CTV P : GTV-P +/-3-5cm cranio caudal +/- 1 cm axially, adapted to anatomical barriers CTV N : adjacent nodal areas PTV : CTV-P and CTV-N +/- 1 cm Techniques : IMRT	If no surgery or refusal
Adjuvant radiotherapy	Dose : 50-54 Gy	In case of incomplete resection or risk factors (extranodal extension, lymphovascular invasion) and if locally advanced tumour
	Volumes CTV P : Surgical bed PTV P : CTV P+/- 1 cm CTV N : nodal adjacent areas Techniques : IRMT	

Legend: GTV- Gross Tumour Volume; CTV- Clinical Target Volume; PTV- Planned Target Volume; P- Primary Tumour; N- Nodes; IMRT- Intensity Modulated Radiotherapy

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axially. Yathiraj used a 1 cm extension for CTV P and N [9]. The adjacent CTV-N areas were taken in some cases, especially if initial involvement [7] and at least areas IV and V [9]. A margin of 0.5-1 cm was used for PTV. In terms of toxicities, radiotherapy was well tolerated [8–10] with no grade more or equal to 3. The early effects found included low-grade mucositis and dermatitis. Late side effects included hypothyroidism and a case report mentioned ventricular tachycardia [11]. Regarding prognostic, overall survival at 5 years was about 40-50% for all histologies and all treatment combined [8,12]. Two registry studies showed a survival improvement over time with more surgery realised [13,14]. A benefit in terms of overall survival was found in several registry analyses by the addition of radiation therapy [12]. Brachytherapy has been used as a curative treatment but also in palliative case for symptoms [15]. In the case of squamous cell carcinoma, the prognosis was worse, around 8-14% at 5 year comparatively to other histologies [7,16,17] . Among the prognostic factors, adenoid cystic carcinoma histology was associated with better local control and survival [8,16] . A dose-effect of radiotherapy greater than 68 Gy was found on progression-free survival in Zeng's series [8]. Performans status (PS), primary surgery, adjuvant radiotherapy and haemoptysis were significantly associated with survival – on the contrary of the use of systemic treatment in Napieralska's series [7]. The incidence was similar between locoregional progressions (17-28%) and pulmonary and bone metastatic progressions (21%) [7,8]. Age≥65 years, ≥1 comorbidities, and palliative treatment have been found as prognostic factors [13]. Other risk factors have also been reported in recent case reports such as HPV 18 [18], previous treatment with radiotherapy [19] or radioactive iodine [20]. A complete response after post radiotherapy progression had been induced by immunotherapy in another case [21].

Discussion

Few data have been published on squamous cell carcinoma of the trachea. Table 2 summarizes the main elements proposed for radiotherapy and systemic treatment in this context, found in the selected studies. In terms of treatment, surgery remains the treatment offered as first-line due to a much more pejorative prognosis in terms of survival if not operable. Exclusive radiotherapy remains for cases of refusal or contraindication to surgery. The better prognostic associated with surgery is described for locally advanced squamous cell carcinoma in other localisation such as larynx-hypopharynx, oesophagus and lung. Adjuvant radiotherapy must be discussed particularly in the case of insufficient margin, extra nodal extension and for some authors if locally advanced tumours [8]. In case of a high volume impossible to adequately cover, an induction treatment before could be discussed. A few cases of induction chemotherapy in the retrospective series have been described without information on their effect. Systemic treatments most often included cisplatin 100 mg/m^2 or weekly – which seems analogous to lung and HNT cancers. Among the other combinations, a case report used carboplatin paclitaxel [22]. No association with immunotherapy was found in case of early stage. A phase II is currently open for rare tumours with a combination of Nivolumab-Ipilimumab (NCT02834013). Radiotherapy was performed using intensity modulation (IMRT) in most series and in photon. No series or cases with proton therapy have been found. A 5-point mask seems the most suitable for the treatment. The dose and fractionation were mostly around 60-70 Gy; a dose higher than 68 Gy could be discussed in view of its association with better local control in Zeng's series [8]. For the volumes, at the level of tumour involvement, the trachea is located under the larynx, with the glottic plane cranially and above the carina. The cricoid and thyroid cartilage represent an anatomical barrier to extension in squamous cell carcinoma of the larynx [23]. It does not necessarily seem appropriate to extend the tumour volume above the latter unless affected. Facilitated diffusion into the tracheal cylinder suggests a cranio-caudal margin larger than the axial one [8]. The integration of adjacent or invaded areas was described in the different series – locoregional recurrences being not uncommon. Few data were found in terms of acute and late toxicity apart from thyroid and respiratory involvement [8,9]. Compared to squamous cell carcinoma, other histologies have different prognoses, notably adenoid cystic carcinomas. Data proposed in this review do not apply to these histologies due to their different extensions, their even rarer incidence, and their response to treatment comparatively to squamous cell carcinoma. Concerning prognostic, local control and survival were relatively low if no surgical treatment despite high doses. Smoking appeared as a factor of poor prognosis in some series. Given the relatively young age and the difference in terms of survival between surgical treatment or not, the opinion of an experienced center seems essential. Two nomograms were developed based on a cohort of 405 patients treated between 1988 and 2015 [24]. Other factors of good prognosis had been considered - (young age, female sex) - allowing aggressive treatments. Lymph node involvement, with a poor prognosis “should justify a more aggressive therapeutic approach. This review presents relatively recent results with description of treatment protocols. Only scarce and heterogeneous data was available, due to the rareness of tracheal carcinomas. The description of the diagnostic work-ups and the place of some imaging methods such as PET that may have revealed lymph node involvement are not detailed. Main data part is ether is in the form of case report or registry study without exhaustive modalities description. Benefits of brachytherapy in terms of survival, local control and toxicities have not been discussed in this review.

Conclusion

Few data have been published on radiotherapy treatment in squamous cell carcinoma of the trachea. Overall survival

Larnaudie A et al., Arch Clin Med Case Rep 2022
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was approximately 14-50% at 5 years depending on histology and treatment performed. The most common extensions are in the oesophagus and thyroid. In the absence of surgical treatment, the prognosis is poorer. Exclusive radiotherapy, preferably with intensity modulation techniques at doses of 60 to 70 Gy, can be associated with systemic treatment. The doses varied between 50 and 54 Gy in the case of adjuvant radiotherapy. The main systemic treatments included a platinum salt mainly administered concomitant to irradiation. The opinion of a specialized center seems important given the rare incidence, the absence of consensual treatment.

Conflict of Interest

None.

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