REVIEW ARTICLE

A Systematic Review Comparing LKB and Alternative NTCP Models for Predicting Radiation-Induced Toxicity in Head and Neck Cancer

Maedeh Sadr[1], Azadeh Amraee[1,2*], Ali Bagherzareh[1]

[1] *Department of Medical Physics, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran*

[2] *Social Determinants of Health Research Center, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran*

*Corresponding Author: Azadeh Amraee

Email: azh.amraee@gmail.com

Received: 27 October 2025 / Accepted: 22 November 2025

Abstract

Purpose: Radiation therapy of the head and neck (HNC RT) is often associated with xerostomia and dysphagia, making it extremely important to predict these toxicities. This review aims to evaluate the Lyman-Kutcher-Burman (LKB) model against alternatives such as relative seriality (RS) for estimating normal tissue complication probability (NTCP) to improve the management of HNC RT-induced side effects.

Materials and Methods: An Extensive literature search was conducted in PubMed, Embase, Web of Science, Google Scholar, and the Cochrane Library to identify published studies between 1991 and 2023 on the above topic. Studies were included if they presented quantitative NTCP models for xerostomia and dysphagia induced by radiation therapy. The key LKB parameters (TD50, m, n) were extracted, and comparative analyses were conducted using the RS and clustering methods based on clinical and dosimetric data.

Results: A total of 27 studies were included, with 20 addressing xerostomia, 6 focusing on esophagitis with dysphagia, and 1 on dysphagia alone. Quality assessment using JBI criteria showed that 21 studies were of high quality, 5 of moderate quality, and 1 of low quality .60-90% of the cases of HNC RT are reported to have xerostomia, which is raised to 100% when salivary glands are involved. Dysphagia occurs in 50-70% of cases, which increases to 90% with chemotherapy. Xerostomia occurs at doses above 40 Gy, and dysphagia at doses above 60 Gy. These are reduced by up to 50% with intensity-modulated radiation therapy (IMRT) and swallowing exercises. The prediction of radiobiological models is around 75-85% for xerostomia and 70-80% for dysphagia. LKB prediction accuracy is at 70-75%; RS achieves 75-80%. Machine learning models show 85-90% accuracy.

Conclusion: Advanced radiation therapy techniques, in combination with validated toxicity prediction models, can improve treatment personalization and reduce the incidence of radiation-induced complications in HNC patients. Future research should focus on refining predictive models, investigating long-term treatment outcomes, and developing novel strategies to protect normal tissues.

Keywords: Radiation therapy; Normal Tissue Complication; Model, Head and Neck Cancer.

DOI:

1. Introduction

Head and Neck Cancers (HNC) refer to a category of malignancies that are quite prevalent, with 890,000 new diagnoses and around 450,000 fatalities annually. HNC encompasses a group of malignancies that originate from various epithelial tissues within regions such as the oral cavity, pharynx, larynx, and other structures of the head and neck [1]. Typical symptoms of HNC include persistent throat pain with difficulty swallowing, neck lumps, etc. [2]. Similar to many other cancer types, radiation therapy serves as the primary treatment approach for head and neck malignancies [3]. Particularly in situations where tumors cannot be surgically resected, this approach becomes highly useful and is also frequently combined with chemotherapy to promote therapeutic success [4].

This is despite new advances in the development and optimization of radiation therapy strategies aimed at minimizing damage while controlling disease [5]. There will still be some resulting side effects of treatment on the healthy Organs At Risk (OARs) [3]. The commonest side effects that may be encountered by patients with HNC undergoing radiation therapy are xerostomia, dysphagia, and mucositis. All of these conditions require additional medical attention and result in compromised quality of life [6]. Xerostomia, or radiation-induced dry mouth, typically occurs when high doses of radiation are delivered to the salivary glands.

Saliva has multiple functions in the oral cavity, including facilitating immune responses through antibodies, providing a means for pH changes, remineralizing demineralized tooth structure with minerals, moistening food to be swallowed, and aiding in taste perception. Patients with functionally reduced salivary glands or xerostomia due to HNC radiation therapy are at risk for fungal infections and dysphagia, altered taste perception, and a sticky oral mucosa. These complications affect swallowing, speech, and taste, which ultimately reduce the quality of life for these patients [7].

Decreased swallowing capability due to difficulty or abnormality is one of the common problems following HNC radiation therapy. Among those patients, dysphagia or difficulty swallowing is most often brought about by radiation-induced inflammation of the esophagus, or esophagitis [8]. Radiation therapy used for tumors of the nasopharynx, oral cavity, Hodgkin's lymphoma, lung, or metastatic sites often exposes the esophagus as an organ at risk, especially when using three-dimensional conformal radiation therapy(3D-CRT) or intensity-modulated radiation therapy (IMRT), leading to side effects such as esophagitis and dysphagia [4]. Dysphagia may further complicate dietary changes, malnutrition, tube feeding dependency, and impact on health-related quality of life [9]. Depending on radiation dose and volume, acute and chronic esophagitis may occur in fewer than 3 months and after 6 months of radiation therapy, respectively [4].

To have effective dose constraints, one must rely on radiobiological models of Normal Tissue Complication Probability (NTCP), which correlate radiation dose with the likelihood of complications in healthy tissues [6]. The other major goal of radiation therapy is NTCP management, which ensures that the prescribed doses are delivered accurately [3]. NTCP modeling is another approach to assess the risk of radiation-induced complications [10]. These models belong to the class of dose-response models and mathematically characterize the probability of a normal tissue complication at a given dose [11]. They transform physical dose distributions into biological dose responses and thereby elucidate tissue-specific radiation sensitivity. Ultimately, accurate modeling of NTCP remains critical to aiding clinicians in making treatment decisions that maximize efficacy and minimize side effects [12].

The model extensively used in predicting the toxicity of radiation treatment is none other than the Lyman-Kutcher-Burman or LKB model [3]. It uses Dose-Volume Histograms (DVH) to analyze dose distributions in OARs and assumes homogeneous responses within the irradiated tissues. The LKB model captures three basic parameters: TD50 (the uniform dose that gives a 50% complication probability), m (the slope or standard deviation around TD50), and n (the volume effect, which indicates the dependence of tissue response on dose volume) [13]. While the LKB model has been widely used due to its simplicity and historical validation, alternative NTCP models, such as the Relative Seriality (RS) model and modern machine learning-based approaches, have

been developed to potentially improve individualized toxicity prediction. Accurate NTCP modeling is crucial in clinical decision-making, as it guides dose constraints, balances tumor control with normal tissue sparing, and ultimately impacts patient outcomes, including quality of life and treatment-related morbidity [12]. By critically assessing both classical and emerging NTCP models, clinicians can better tailor radiotherapy plans to minimize complications such as xerostomia, dysphagia, and esophagitis.

While several systematic reviews and modeling studies have addressed individual complications of head and neck radiotherapy, there is a lack of comprehensive evaluation specifically focusing on the performance and limitations of the Lyman-Kutcher-Burman (LKB) model across multiple radiation-induced toxicities. Most previous publications have either investigated xerostomia or dysphagia in isolation, without integrating esophagitis as a clinically relevant toxicity in this context. The present review provides a systematic synthesis of evidence regarding the predictive ability of the LKB model for xerostomia, dysphagia, and esophagitis, highlighting dose–volume relationships and parameter variations across studies. By stratifying the literature according to specific complications and critically assessing methodological heterogeneity, this review uniquely emphasizes the strengths and weaknesses of the LKB model as a predictive tool for treatment planning in head and neck cancer. This focused perspective distinguishes our study from earlier reviews and provides a framework for improving personalized radiotherapy strategies.

2. Materials and Methods

2.1. Study Selection Criteria

This systematic review examined the complications of radiation therapy for HNC that result in xerostomia, dysphagia, and esophagitis. Studies were included if they were case-control, cross-sectional, or cohort studies providing quantitative data on these complications. The exclusion criteria encompassed case reports, case series, reviews, abstracts, and articles that did not address radiation therapy complications. Studies involving treatments other than radiation therapy, such as chemotherapy alone or surgery, were also excluded. Understanding the side effects associated with radiation therapy is critical for effective patient management and supportive care, as head and neck radiation therapy significantly affects salivary function, swallowing ability, and mucosal health.

2.2. Search Strategy and Data Sources

A systematic literature review was conducted following PRISMA guidelines to ensure transparency and reproducibility. Studies published from 1991 to 2025 were identified through comprehensive searches of major databases, including PubMed, Embase, Web of Science, Scopus, Google Scholar, and the Cochrane Collaboration. Advanced Boolean operators (AND, OR) were applied to refine search strings based on prior research and expert recommendations, using keywords such as "radiotherapy OR radiation therapy," "head and neck cancer," "xerostomia," "dysphagia," "swallowing dysfunction," and "esophagitis." Gray literature was explored via Grey Matters and additional Google Scholar searches, and a PICO framework guided the search within the OVID database.

Data extraction was independently performed by two reviewers using a standardized PRISMA form, and disagreements were resolved through discussion and consensus. Study quality was assessed using the JBI critical appraisal checklist, with inter-rater reliability confirmed by Cohen's kappa ($\kappa = 0.82$), indicating strong agreement.

Ultimately, 27 studies met the inclusion criteria, comprising 20 addressing xerostomia, 6 focused on esophagitis with dysphagia, and 1 investigating dysphagia alone. Comparative analyses were subsequently conducted across classical NTCP models (LKB and RS) and advanced machine learning-based models, integrating quantitative parameters (TD50, m, n), clinical endpoints, and dosimetric data. This structured synthesis ensures that variations in study quality are accounted for and allows a robust evaluation of predictive performance and applicability in clinical decision-making.

2.3. Screening and Eligibility Assessment

Two independent reviewers applied strict inclusion and exclusion criteria to maintain impartiality and

reduce selection bias. The criteria limited the search to publications between 1991 and 2025 to capture the most current and pertinent evidence. Each study was appraised using a methodological quality checklist adapted from the Joanna Briggs Institute (JBI) critical appraisal instruments. This checklist evaluates key elements, including study design, data collection methods, analysis, participant selection, result clarity, bias, eligibility criteria, and reproducibility, comprising 11 essential items. Studies had to satisfy at least four of these items to qualify for inclusion. To further reduce bias, two researchers not involved in the study conducted a blinded assessment using the checklist [14]. Excluded articles were literature reviews, conference abstracts, doctoral dissertations, technical reports, Monte Carlo simulations, phantom studies, and studies irrelevant to the subject. After duplicates were removed, studies were initially screened by title and abstract, followed by full-text review based on the predefined criteria and quality assessment.

2.3. Data Extraction

Data extraction was independently conducted by two reviewers using a standardized and organized form, with a third reviewer stepping in to resolve any disagreements. The collected data encompassed: study information (including author, publication year, cancer type, and sample size), patient characteristics (age range, gender, and follow-up time), details of radiation therapy (such as radiation type, total dose, fractionation schedule, biological effective dose, and alpha/beta ratio), treatment specifics (including technique, treatment planning system, radiation energy, and percentage dose difference in planning target volume (PTV) with and without contrast), as well as modeling parameters (LKB model variables like TD50, m, and n), along with documented complications like xerostomia, dysphagia, and esophagitis.

2.4. Screening and Eligibility Assessment

All retrieved articles underwent a thorough multi-stage screening process. Initially, two independent reviewers (M.S. and A.B.) screened the titles and abstracts for relevance. Studies deemed relevant were then examined in full text. Any disagreements were first resolved through discussion, and if consensus was not reached, a third reviewer (A.A.) was involved to maintain consistency. This eligibility evaluation was guided by a predefined checklist emphasizing methodological rigor to reduce selection bias. To qualify for final inclusion, studies needed to demonstrate evidence of dose-response relationships related to radiation-induced xerostomia, dysphagia, or esophagitis. Articles scoring below 50% on at least four key quality criteria, such as study design, data collection, analysis, and participant selection, were classified as low quality and excluded from the final review.

3. Results

Initially, a total of 370 records were identified. Preliminary screening based on titles and abstracts had 257 studies picked for full-text evaluation. Of those, 224 were excluded for different reasons, mostly being conference abstracts or duplicate datasets. Ultimately, 27 studies fulfilled eligibility criteria and were included in the systematic review (Figure 1). Of these, 20 studies specifically evaluated radiation-induced xerostomia. Regarding dysphagia, 7 studies were identified; among them, one directly focused on dysphagia, while the remaining six investigated radiation-induced esophagitis, which is a common precursor leading to dysphagia. Since our primary endpoint was dysphagia, studies exclusively addressing esophagitis were also considered relevant to this complication.

According to the review table, there have been numerous studies on NTCP models about radiotherapy-induced dry mouth in HNCs. The reviewed studies varied greatly in patient population characteristics; the age range of participants ranged from 2 to 72 years, and the number of samples ranged from 10 to over 500 patients. Most of these studies focused on patients with HNC who underwent radiotherapy with IMRT or 3DCRT techniques. In terms of NTCP model parameters, the LKB method has been most widely used. The TD50 value (dose at which there is a 50% probability of complication) has been reported in various studies between 28 Gy and about 114 Gy, usually observed in the range of 30 Gy to 40 Gy for salivary glands, especially the parotid. Also, the parameters m (slope of the dose-response curve) and n (dose-volume sensitivity measure) were

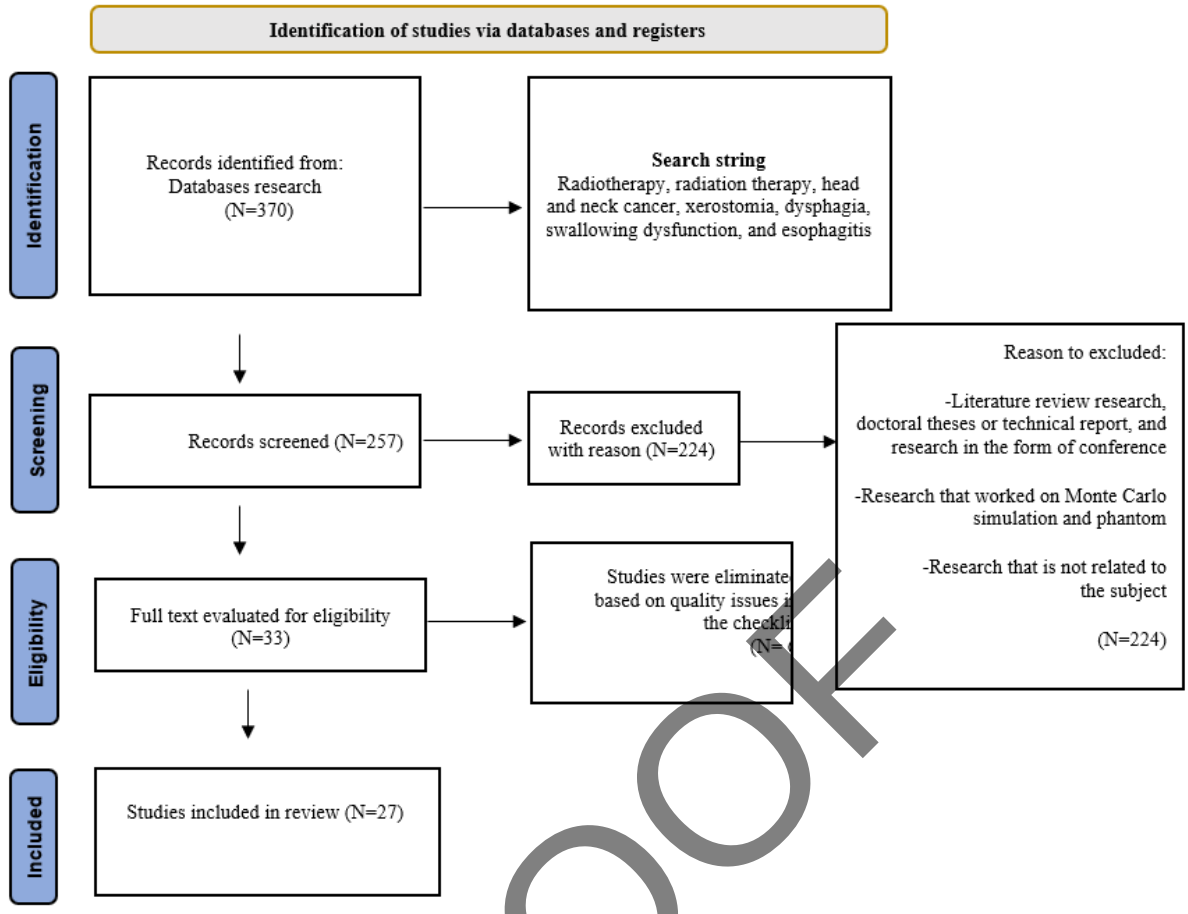

Figure 1. Identification of studies via databases and registers

approximately in the range of 0.3 to 1 in most studies. Most studies considered α/β to be 3 Gy to calculate the biologically effective dose (BED). Salivary gland function was significantly affected after radiotherapy; an average dose of about 39.9 Gy to the salivary glands was associated with a 50% probability of a decrease in salivary function to less than 25% of the pre-treatment level [15]. The decrease in salivary gland function and salivary flow rate often remained persistent over time, although a partial improvement trend after radiotherapy was also reported in some studies. Also, IMRT was more effective than 3DCRT in reducing NTCP and the severity of xerostomia complications, which was confirmed in the studies of Eisbruch [16], Mesbahi [17], and others.

The prevalence and severity of xerostomia in the studied patients varied and were reported in the grades 1 to 3 range. For example, Marzi *et al.* [18] showed that 66% of patients experienced grade 3 complications in the first 3 months after treatment, which decreased to 27% by 12 months. Gabryś *et al.* [19] showed that 67% of patients experienced mild to severe (G1+) xerostomia and about 15–20% experienced moderate to severe (G2+) xerostomia. Kanehira [20] also reported a prevalence of moderate to severe xerostomia of 33.2%. NTCP models have been able to provide a reasonable prediction of the likelihood of xerostomia, and this can be useful in the optimal design of radiotherapy programs to reduce side effects. Changes in treatment scheduling, including intervals and fractional doses, as well as the use of more advanced techniques such as IMRT, VMAT, and Tomotherapy, are effective in reducing side effects. Some studies have reported improvements in salivary gland function and quality of life in patients in the months following treatment, suggesting the possibility of improved salivary function. Follow-up periods in these studies have varied and ranged from 3 months to 5 years, indicating that radiotherapy-induced complications can be observed in the short and long term. Studies with longer follow-up periods, such as Braam [21], have examined changes in salivary gland function and severity of complications over time and have shown the possibility of relative improvement in function (Table 1, 2).

Table 1. Review of studies evaluating NTCP model parameters for radiation-induced xerostomia in head and neck cancer radiotherapy

Author	Mean age	Dose (Gy)	Dose per fraction	TD_{50} (Gy)	m	n	α/ß (Gy)	BED (Gy)	Follow up (month)	Radiation Modality	Complication
Xerostomia											
Result:---											
C. BURMAN (1991)				46	0.18	0.7	3				Xerostomia
Results: ---											
AVRAHAM EISBRUCH (1999)	55	64	1.8-2	28.4	0.18	1	3	102.4	12	3D CRT & IMRT	Xerostomia
Result: Total patients: 88 1.for 96 glands with saliva output data available at 12 months, 37 had stimulated output at or below 25% of the baseline pre-RT output, which were considered to represent "severe complications" 2. The NTCP values generally appeared as either 100% or 0%, with merely 12 glands exhibiting NTCP values ranging from 5% to 95%											
JUDITH M. ROESINK (2001)	57	A* B* C* D*	2 Gy	31(6 week) 35(6 mth) 39(12 mth)	0.54(6 week) 0.46(6 mth) 0.45(12 mth)	1	3	A** B** C** D**	6 weeks 6 mth 12 mth		Salivary Gland toxicity Change in Parotid Gland Function
A*: 46-50: for clinically negative, undissected necks that were susceptible to microscopic metastatic disease **BED (A): 76.6-83.3 B*: 50–70: for postoperative tumor beds or dissected neck sites ** BED (B): 83.3-116.6 C*: 66–70: for tumors treated primarily with radiation ** BED (C): .110-116.6 D*: 40: for Six patients with Hodgkin's disease or non-Hodgkin's lymphoma ** BED (D): 66.6											
Result: Total patients: 108 A parotid flow ratio of 25% post-treatment was indicative of complications such as xerostomia.											
C. SCHILSTRA (2001)		46-70	2 Gy	38	0.26	1.3	3	76.6-116.6		3D CRT	xerostomia, impeded oral functioning, oral infections, and dental caries
Result: Total patients: 15											
PÈTRA M. BRAAM (2005)	56	66		34(6 week) 40(6 mth) 42(12 mth) 46(5 yr)	0.37(6 week) 0.33(6 mth) 0.37(12 mth) 0.53(5 yr)	1	3	110	57	3D CRT	Xerostomia or Change in Parotid Gland Function
Result: Total patients: 52											
V A Semenenko (2008)			2	31.4	0.53	1	3				Xerostomia
Result:---											
ANTONETTA C. HOUWELING (2009)				39.4	0.42	1.13	if 3 if 10			3D CRT & IMRT	Xerostomia Reduction in salivary flow
Result: Total patients: 347											
Tim Dijkema (2009)	*	**	***	****	†	††	3	†††		3D CRT & IMRT	Xerostomia or Change in Parotid Gland Function
*In Michigan: 54, In Utrecht: 58 ** In Michigan: 60-75, In Utrecht: CRT:50-70 to GTV, IMRT:69-70 *** In Michigan: 60-75, In Utrecht: CRT:50-70 to GTV, IMRT:69-70 **** Michigan: 40.5, Utrecht: 39.7, combined analysis: 39.9 , 39.4 † Michigan:0.36, Utrecht:0.44, combined analysis: 0.40, 0.42 †† Michigan:1, Utrecht:1, combined analysis:, if 1, if 1.13 ††† In Michigan: 96-120, In Utrecht: CRT:83.3-116.6, IMRT:115-116.6											
Result: Total patients: 222 At a mean dose of 39.9 Gy, there is a 50% probability of parotid gland flow reduction to <25% of the pre radiotherapy outflow.											
SIMONA MARZI et al. (2009)	57.5		2 Gy	21.4(3mth) 27.8(6mth) 41.6(12mth)	0.57(3mth) 0.49(6mth) 0.45(12mth)	1	3		12.8	IMRT	salivary gland toxicity (Grade3)
Result: Total patients: 59 in 3 mnth (total 59 patient): 5 patient grade 1 / 15 patient grade 2 /39 patient grade 3 in 6 mnth (total 51 patient): 1 patient grade 0 / 8 patient grade 1 / 17 patient grade 2 / 25 patient grade 3 in 12 mnth (total 37 patient): 2 patient grade 0 / 8 patient grade 1 / 17 patient grade 2 / 10 patient grade 3 in 18 mnth (total 24 patient): 2 patient grade 0 / 5 patient grade 1 / 12 patient grade 2 / 5 patient grade 3 in 24 mnth (total 21 patient): 3 patient grade 0 / 5 patient grade 1 / 8 patient grade 2 / 5 patient grade 3											
Tsair-Fwu Lee (2012)	53	52-70.8	1.8-2	quality of life: 44.1 Salivary excretion factors: 43.6	quality of life: 0.11 Salivary excretion factors: 0.18	1	3		46.8	IMRT	Salivary gland toxicity
Result: Total patients: 31 Grade 3 toxicity incidence decreased from 66% at 3 month to 27% at 12 month after RT											

Author	Mean age	Dose (Gy)	Dose per fraction	TD_{50} (Gy)	m	n	α/ß (Gy)	BED (Gy)	Follow up (month)	Radiation Modality	Complication
Tsair-Fwu Lee (2013)	*	**	***	37.8 (3mth) 43.9 (12mth)	0.59 (3mth) 0.48 (12mth)	1	3		3 & 12	IMRT (SIB & SQM)	Grade +3 Xerostomia
* 54:HN squamous cell carcinoma, 49: nasopharyngeal carcinoma ** HN squamous cell carcinoma: PTV1: 54–77.4 Gy, PTV2: 48–72 Gy, PTV3: 41.4 Gy ،nasopharyngeal carcinoma: PTV1: 65–77.4 Gy, PTV2: 48–72 Gy, PTV3: 41.4 Gy *** simultaneous integrated boost (SIB):1.6-2.12, sequential mode (SQM):1.8-2.0											
Result: Total patients: 237 Grade 3+ xerostomia incidence at 1 year was only ~1% or ~2%											
Asghar Mesbahi (2017)		3D CRT:70 IMRT: 72	2	28.4	0.18	1	3	86.4		3D CRT & IMRT	Xerostomia
Result: Total patients: 10 The NTCPs for the parotid glands, thyroid gland, spinal cord, TMJ, and mandible were significantly reduced in the IMRT plans, in contrast to the levels observed in the 3DCRT plans											
Hubert Szymon Gabryś (2017)	60	*		**	***	1	3		6± 3 12±3	IMRT, Tomotherapy	****
* Ipsilateral parotid: 25.4, contralateral parotid: 18.7 ** xerostomia G1+ (mild to severe): 10.7 -13.6, xerostomia G2+ (moderate to severe): 42.8 - 64.8 *** xerostomia G1+ (mild to severe): 10.7 -13.6, xerostomia G2+ (moderate to severe): 42.8 - 64.8 **** (1) moderate to severe xerostomia quantified by grades 2 and higher (G2þ), (2) mild to severe xerostomia quantified by grades 1 and higher (G1þ)											
Result: Total patients: 153 Mild to severe (G1+) xerostomia prevalence at both 6 and 12 months was 67%. Moderate to severe (G2+) xerostomia prevalence at 6 and 12 months was 20% and 15%, respectively											
Panayiotis Mavroidis (2017)		60		*	**	1	3			VMAT	Xerostomia (12mth)
* Combined Contralateral glands: 26.9, Contralateral parotid: 21.9, Contralateral submandibular: 47.7 ** Combined Contralateral glands: 0.63, Contralateral parotid: 0.78, Contralateral submandibular: 0.70											
Result: Total patients: 43 Just 24% of patients experienced moderate to severe xerostomia at six months post-radiotherapy, according to the EORTC QLQ-H&N35. ROTG/EORTC G2+ xerostomia in only two patients (3%).											
P. Mavroidis (2019)		60		*	**	***	3			IMRT	Xerostomia
*1) contralateral parotid: 67, 2) contralateral, glands (parotid and submandibular glands combined) :56 **1) contralateral parotid:0.58, 2) contralateral, glands (parotid and submandibular glands combined) :0.56 ***1) contralateral parotid: 0.01, 2) contralateral, glands (parotid and submandibular glands combined) :0.12											
Result: Total patients: 120 Toxicity was 21/35 patients in 6 month after RT, Toxicity was 15/33 patients in 12 month after RT											
Ming Chao (2019)		66	2.2	*	**	***	3	114.4			Xerostomia
* Mean dose model: 39.47, 39.90, Full LKB Model: 27 ** Mean dose model: 0.408, 0.400, Full LKB Model:0.77-0.57 *** Mean dose model: if 1, if 0.908, Full LKB Model: 0.9											
Result: Total patients: 75											
Panayiotis Mavrodits (2021)	61	25-40	2-3	A. 23.4 B. 61.2	A. 0.89 B. 0.77	A. 1 B. 1	3		1,3,6	3D-CRT	A.Xerostomia B.Dry eye
Result: Total patients: 55 19 (35%) had≥20 point increase in xerostomia score, 11 (20%) had≥2 point increase in xerostomia bother score, 13 (24%) had≥2 point increase in SESoD (e Subjective Evaluation of Symptom of Dryness) score											
Takahira kanehira (2021)		*	**	***	****	†	††	†††	††††	VMAT with CBCT	xerostomia - dysphagia - oral mucositis
* 54.25 in 35 frac for SIB plan., 46 Gy in 23 frac for sequential plan. **1.55 for SIB plan, 2. for sequential plan *** 1.55 for SIB plan, 2 for sequential plan **** A. 1.129, B. 0.452, C. 0.475, D. 0.368, E. 1.124, F. 0.834, G. 0.394 † A. 1, B. 1, C. 0.166, D. 0.202, E. 0.001, F. 1, G. 1 ††10 for OC, 3 for CPG ††† 82.27 for SIB plan, 75 for sequential plan ††††3 monthly for first year, 4 monthly for second year, 6 monthly for following years											
Result: Total patients: 322 Xerostomia E. 107 (33.2%), F. 61 (18.9 %), Dysphagia, A. 211(65.5%), B. 93(28.9%), G. 50 (15.5%), oral mucositis, C. 198 (61.5%), D. 80 (24.8%)											
Pratik Samant (2023)				47	0.55	1	3		6		Xerostomia
Result: Total patients: Training set patients:194, Test patients: 76											
Derek K. Smith (2023)	59.8			39.2	1.1	1	3			IMRT or VMAT	radiation induced salivary gland hypofunction
Result: Total patients: 510 mean post-treatment salivary flow rate of 0.57 g/min after one year (compared to 1.47 g/min before treatment)											

Abbreviations: BED – biologically effective dose; Gy – Gray; RT – radiotherapy; IMRT – intensity-modulated radiotherapy; 3D CRT – three-dimensional conformal radiotherapy; LKB – Lyman-Kutcher-Burman; RS – relative seriality; TD_{50} – dose at 50% complication probability; NTCP – normal tissue complication probability

Table 2. Review of studies evaluating NTCP model parameters for radiation-induced dysphagia and esophagitis in head and neck cancer radiotherapy

Author	Mean age	Dose (Gy)	Dose per fraction	TD_{50} (Gy)	m	n	α/ß (Gy)	BED (Gy)	Follow up (month)	Radiation Modality	Complication
Esophagitis											
Result:---											
C. Burman (1991)				68	0.11	0.06					Clinical stricture/perforation of Esophagus
Result:---											
Jose Belderbos -1 (2005)	69	49.5-94.5	2.25-2.75	47	0.36	0.69	10	60.63-115.76	2 mth after treatment	3D CRT	Acute esophagitis & Dysphagia Grade +2
Result: Total patients: 156 Acute esophageal toxicity of grade 2 or higher was observed in 27% (n=42) of the patients, with nine individuals experiencing grade 3 toxicity and one individual grade 4. All 10 patients experiencing grade R3 esophageal toxicity underwent concurrent CRT.											
Jose Belderbos - 2 (2005)		60.8-94.5	2.25	80	0.06	0.34	10	for dose 80Gy: 93Gy	12	3D CRT	Dysphagia Grade 2,3 & Late Esophagus toxicity +2
Result: Total patients: 88											
Olivier Chapet (2005)		65.1-102.9	2.1	51	0.32	0.44	10	78.77-124.5	3	CRT	Acute esophagitis & Dysphagia
Result: Total patients: 101 Sixteen of the 101 patients developed a grade 2–3 acute, esophagitis (13 G2, 3 G3, no G4 or 5)											
Jian Zhu (2010)		61	2	*	**	***	10	73.5	every 3 mth after RT	3D CRT	Acute Esophagitis in lung cancer
* RT without concomitant CT: 46, RT with concomitant CT: 36 ** RT without concomitant CT: 0.15, RT with concomitant CT: 0.42 *** RT without concomitant CT:0.29, RT with concomitant CT: 0.09											
Result: Total patients: 157 35 (22%): grade 2 AE, 20(13%): grade 3 AE, 0: grade 4 & 5 AE, 24% of group1 (RT alone or sequential CRT): grade 2 or 3 AE, 52% of group2 (RT combined with concomitant chemotherapy): grade 2 or 3 AE											
W. Uijterlinde (2014)	63	66	2.75	76.1	0.03	0.03	10	84.15	3 mth after treatment	IMRT	late esophagus toxicity
Result: Total patients: 171 Out of 171 patients, 11 (6%) experienced severe late esophageal toxicity after a median follow-up period of 33 months (95% CI 29–37), with a median overall survival time of 24 months (95% CI 16~32).											
Julian Roers (2023)	59	*	1.8-3	**	***	†	3	††		ISRT employing the IMRT method or PBT	†††
* RT with Chemo:24-54 (mean:40.3), only Rt:22.5-45 (mean:34.1) ** 1) Esophagitis with Dysphasia:58.0, 2)only Dysphasia:77.5 *** 1)Esophagitis with Dysphasia:0.47, 2)only Dysphasia:0.95 †1)Esophagitis with Dysphasia:0.06, 2)only Dysphasia:0.06 †† RT with Chemo:47.55, only Rt: 40.23 ††† Esophagitis/with Dysphagia/only Dysphagia/Nausea/Pneumonitis/Pericarditis/Myelitis											
Result: Total patients: 114 Lowering radiation doses from 40 Gy to 30 Gy resulted in a reduction in the incidence of three acute side effects, particularly grade 1 esophagitis. (NTCP40Gy = 17.4% ± 9.1% vs. NTCP30Gy = 12.3% ± 5.8%), esophagitis grade 2+ (NTCP40Gy = 5.4% ± 3.3% vs. NTCP30Gy = 3.3% ± 1.8%), and nausea grade 1 (NTCP40Gy = 5.5% ± 3.2% vs. NTCP30Gy = 3.5% ± 1.8%), respectively											

Abbreviations: BED – biologically effective dose; Gy – Gray; RT – radiotherapy; IMRT – intensity-modulated radiotherapy; 3D CRT – three-dimensional conformal radiotherapy; LKB – Lyman-Kutcher-Burman; RS – relative seriality; TD_{50} – dose at 50% complication probability; NTCP – normal tissue complication probability

In conclusion, NTCP models based on LKB parameters, combined with average doses of approximately 35 to 40 Gy to the salivary glands, are capable of reasonably and reliably predicting xerostomia in patients with HNC. The prevalence and severity of this complication strongly depend on the type of treatment technique, the total dose delivered, and the average dose imposed on the salivary glands. The use of advanced radiotherapy techniques such as IMRT and VMAT is more effective in reducing complications than traditional 3DCRT techniques.

Also, longer follow-up periods indicate the possibility of partial return of salivary gland function and improvement of xerostomia symptoms over time. Thus, NTCP models can be used as a valuable adjunct tool in radiotherapy treatment planning to reduce xerostomia complications.

4. Discussion

Several clinical studies have shown that head and neck radiation therapy induces xerostomia in 60-90% of patients, with the incidence rising to nearly 100% when the treatment fields include the major salivary glands. This high prevalence occurs because radiation doses disrupt the delicate acinar cells responsible for saliva production, particularly in the parotid glands, which are highly radiosensitive. Severity typically correlates with the average dose to the parotid glands, with most patients experiencing significant dryness if the glands receive more than 26 Gy [15].

In addition to xerostomia, approximately 50-70% of patients develop radiation-induced dysphagia due to fibrotic changes in the swallowing muscles and neural structures. When radiation is combined with chemotherapy, as is often the case in advanced cases, the swallowing complication rate increases to 90% because chemotherapy potentiates radiation damage to mucosal tissues. The critical dose thresholds are well established: doses above 40 Gy to salivary tissues reliably cause xerostomia, while doses above 60 Gy to the pharyngeal constrictors and laryngeal elevators typically result in persistent dysphagia [22-25].

Advanced radiotherapy methods like IMRT have revolutionized outcomes by allowing dose sculpting around critical structures. When combined with proactive swallowing exercises supervised by speech pathologists, these advanced techniques can reduce complication rates by up to 50%. The exercises work by maintaining muscle tone and range of motion during treatment, while IMRT spares key anatomical structures through precise dose modulation [26, 27].

Radiobiological modeling has become increasingly sophisticated in predicting these complications. Current models, such as the LKB and RS models, can predict the development of xerostomia with 75-85% accuracy by analyzing salivary gland dose-volume histograms. For dysphagia prediction, models achieve 70-80% accuracy by evaluating dose distributions to swallowing structures. The traditional LKB model shows a respectable 70-75% accuracy, but is being replaced by the Relative Seriality model (75-80% accuracy), which better accounts for tissue organization. Most promising are machine learning algorithms that integrate dosimetric, clinical, and radiomic data to achieve 85-90% predictive accuracy by identifying subtle patterns that humans may miss [28, 29].

These predictive models are becoming clinically indispensable for several reasons. First, they allow radiation oncologists to personalize treatment plans based on individual risk profiles. Second, they facilitate early intervention for high-risk patients. Third, they provide quantitative benchmarks for comparing treatment techniques. However, challenges remain in accounting for anatomical changes during treatment and in incorporating emerging biomarkers of radiosensitivity. Ongoing research focuses on dynamic models that adapt to treatment response and incorporate genetic susceptibility data for truly personalized risk prediction [30, 31].

Radiotherapy, while effective in tumor control, can also damage adjacent healthy tissues, leading to acute or late toxicities. Acute effects, occurring within 90 days, include mucositis, dermatitis, dysphagia, odynophagia, and taste loss, whereas late complications may involve xerostomia, osteoradionecrosis, fibrosis, thyroid dysfunction, trismus, and pharyngoesophageal stenosis [32].

Among these, xerostomia and dysphagia are the most prevalent and clinically significant, as they impair swallowing, increase the risk of oral infections, and markedly reduce patients' quality of life.

Research indicates that effective management of radiation-induced complications through various strategies can significantly enhance patient outcomes. Quantitative models, such as the LKB model, along with more advanced frameworks like the Relative Seriality (RS) and clustering-based models, are essential tools for predicting the likelihood of toxicity. Models such as LKB, RS, and clustering approaches contribute significantly to radiotherapy planning by predicting toxicity, supporting individualized treatment, improving risk stratification, and facilitating clinical decision-making. As technology advances, these models continue to evolve, offering increasing potential for treatment optimization [33, 34].

In contrast, the RS model incorporates the structural organization of tissues and predicts complications based on the volume of tissue irradiated at specific dose thresholds [35]. Personalized treatment planning

and further improved quality of life after treatment are made feasible through the integration of patient- and tumor-specific characteristics, including radiosensitivity of surrounding healthy tissues, into models [33, 36]. Studies have shown that the LKB model provides equivalent or better results than more complex machine learning models [34].

Comparative analysis of various studies indicates that the LKB model is the most commonly applied approach for predicting dysphagia-related complications in radiation therapy. However, the performance of the model varies between studies. For example, a patient study by Hubert Szymon Gabryś [19] and Tsair-Fwu Lee [37], the latter being a QUANTEC guideline–based validation using quality-of-life questionnaire datasets for parotid gland dose constraints, showed that the LKB model had a high capacity to predict mild xerostomia (G1+), as evidenced by a high area under the curve (AUC = 0.69–0.76), but the model's performance in predicting more severe complications (G2+) was comparatively low.

The RS model, as studied in the research of Panayiotis Mavroidis [38], had a better agreement with clinical data compared to the LKB model, especially in the sensitivity analysis of the volume of irradiated tissue. The model was better at predicting small volumes of low-dose changes. Also, in the research by Ming Chao [39], the clustering model achieved very accurate predictions by examining dose patterns within the salivary glands and showed a strong correlation with NTCP ($r \approx 0.95$), emphasizing the importance of dose patterns in reducing complications.

A comparison of these models indicates that the LKB model is a basic tool suitable for predicting minor complications. However, RS and other clustering models may be more appropriate for in-depth analysis and prediction of serious complications.

Which model to choose to accurately predict common complications in radiation therapy patients will depend on the type of complication and the tissue structure being analyzed. This, in turn, would help radiation oncologists and medical physicists to provide more accurate input for treatment planning.

Therefore, the current study reviews studies that have used the LKB model to predict xerostomia and dysphagia complications.

Xerostomia is one of the most common complications in HNC patients receiving radiotherapy, primarily caused by radiation exposure to the salivary glands, especially the parotid and sublingual glands [40]. Salivary gland dysfunction can begin within the first week of treatment, with flow decreasing by 50–60% initially and to about 20% of baseline by the end of seven weeks, often persisting long-term, though partial recovery may occur within two years [24, 41]. Xerostomia leads to taste alterations, dysphagia, oral infections, and impaired speech and chewing, thereby reducing quality of life [41, 42].

Another major toxicity is radiation-induced esophagitis, which may present acutely (within 90 days) or chronically (after two months). This condition, often manifesting as dysphagia or odynophagia, significantly compromises nutritional intake and can result in malnutrition, aspiration-related infections, and psychosocial distress [43-45]. Dysphagia typically appears within four weeks of treatment initiation and may persist for up to two years [44].

Radiation-induced toxicities, including xerostomia and dysphagia, significantly compromise quality of life in patients with head and neck cancer. Accurate prediction of these complications is crucial for personalized treatment planning, enabling clinicians to minimize adverse effects while ensuring tumor control. By systematically reviewing NTCP models, we aim to highlight their potential to guide clinical decision-making and optimize patient outcomes.

Next, we consider a number of important factors that affect the prediction of these complications.

4.1. Number of Patients

One of the most important parameters in assessing the accuracy and generalizability of NTCP models is the number of patients in the study. A larger sample size increases statistical power, model reliability, and generalizability, and allows for more specific analysis, ultimately leading to a better understanding and management of these common complications in clinical practice. Studies with larger sample sizes

provide more stable estimates of complication rates. Greater statistical power allows for better detection of effects and associations between outcomes, such as the presence of xerostomia and dysphagia [46].

A larger number of patients covers a greater variety of patient demographics, tumor sites, treatment modalities, and comorbidities. This heterogeneity facilitates an understanding of the contribution of various factors to post-radiation therapy complications. For example, the incidence of xerostomia is highly variable depending on treatment factors and patient history, suggesting that larger studies can elucidate these determinants [46, 47].

In addition, with more data, researchers can develop and validate more robust predictive models for complications such as xerostomia and dysphagia. Models such as NTCP benefit from larger datasets, allowing for better differentiation between patients who will and will not experience complications [48, 49]. This is critical for optimizing treatment plans and improving patient outcomes.

Results from larger study groups are more likely to be relevant to larger patient populations. This is particularly important in HNC, where treatment success can vary widely depending on individual factors [50, 51].

The studies reviewed here included different numbers of patients. For example, the study by Pratik Samant [52] included 270 patients divided into training and test groups. Similarly, Hubert Szymon Gabryś [19] conducted a study with 153 patients, while Tsair-Fwu Lee [37] analyzed data from 237 patients. Studies with smaller numbers of patients, such as Asghar Mesbahi's [17] 10 patients, were more limited in statistical analysis and applicability of the results. Julian Roers [53] studied 114 patients with non-Hodgkin's lymphoma. W. Uijterlinde [54] also analyzed 171 patients with advanced-stage NSCLC, which provided an adequate sample size for statistical analysis. Although this study primarily focused on thoracic esophageal radiosensitivity in lung cancer patients, its findings offer general insights into radiation-induced esophageal toxicity. Nevertheless, anatomical and biological differences between the cervical esophagus (relevant to HNC) and the thoracic esophagus should be considered when extrapolating these results. In comparison, the study by Elahe Fathipour [8], which included only 50 head and neck cancer (HNC) patients, may limit the generalizability of findings due to the relatively small study population.

The analysis of patient numbers suggests that studies with larger sample sizes, such as W. Uijterlinde [54], are more likely to provide accurate data and contribute to the validity of the model results. The variation in sample size may partially explain the observed differences in LKB model parameters between studies. A review of these studies highlights that increasing the number of patients reduces statistical error and improves the predictive power of the models. Notably, in the study by Derek K. Smith [42], which included 510 patients, the neural network model demonstrated superior predictive performance compared to the LKB-based models. Specifically, the neural network achieved AUC values ranging from 0.75 to 0.83, while the LKB models reported lower AUCs (0.70–0.80 for fitted models and 0.67–0.77 for literature-based models). These results highlight the advantage of larger datasets in improving complication prediction and making model evaluations more precise.

4.2. Age and Sex of Patients

The association between age and the risk of xerostomia and dysphagia following radiation therapy is complex and influenced by multiple factors. In general, advancing age correlates with a higher risk of both complications. Studies indicate that individuals aged 61 and above are particularly vulnerable, likely due to reduced salivary gland function and overall physiological decline [55]. As patients age, factors such as health problems, medications, and other treatments can increase the severity of radiation-related side effects. Age-related decline in tissue elasticity contributes to increased vulnerability in older patients, making them more prone to complications like xerostomia and dysphagia [50, 56]. Therefore, older patients are more affected by these side effects and require careful consideration in treatment planning and follow-up care to improve their quality of life.

The research by Julian Roers [53] did not indicate the effect of age on xerostomia, although it was observed that the age factor could lead to xerostomia

due to decreased salivary gland function. Elahe Fathipour's study [8] also reported a higher incidence of xerostomia among older individuals. The findings revealed that elderly patients received a greater mean dose to the salivary glands, which may partly explain the increased risk of xerostomia in this group. The moderate dose to the cervical esophagus and pharyngeal constrictor muscles (V40-V55) was another cause of dysphagia in the elderly. There was no apparent difference in prevalence between the sexes. The study by Olivier Chapet [57] emphasized the effects of dose-volume parameters rather than a direct relationship between xerostomia and age or sex. It was found that dysphagia was more pronounced in those who received high dose volumes of over 20% in the esophageal region. Literature suggests that xerostomia may be more pronounced in older patients due to increased susceptibility of salivary glands to radiation injury. However, the influence of sex remains unclear, with radiation dose being the primary determinant of this complication. The results of W. Uijterlinde [54] also confirmed that older patients were more often affected by both acute and chronic dysphagia. They also mentioned that radiation doses greater than 75 Gy and fractional doses greater than 2.75 Gy resulted in severe dysphagia in these patients. However, they did not mention any sex disparity in their survey.

In general, age is considered an important predictor of xerostomia and dysphagia, especially in elderly patients due to their impaired tissue repair capacity. However, the influence of sex in these complications is not as pronounced as the influence of age, and dose-related and volumetric parameters of radiation therapy are more decisive in their development.

4.3. Total Dose & Dose per Fraction

The total radiation dose and the dose delivered per fraction are key predictors of xerostomia and dysphagia after head and neck radiation therapy. Evidence suggests a dose-dependent effect, with the risk of dysphagia rising by approximately 19% for every additional 10 Gy administered [16]. Limiting radiation exposure to swallowing-related structures, especially the pharyngeal constrictor muscles, is considered crucial. Studies indicate that maintaining the mean dose to these muscles below 50 Gy can help preserve better swallowing function [16, 50]. The dose per fraction also influences the severity of side effects.

Larger fractions increase the risk of acute toxicity and may inhibit the process of healthy tissue recovery between fractions. The overall duration of treatment, which depends on the number of fractions, plays a role in both patient recovery and symptom control. A longer treatment course with a lower daily dose may result in tissue healing with fewer serious complications than would occur with shorter courses and higher daily doses. High-precision modalities such as IMRT enable accurate tumor targeting while minimizing radiation to swallowing-related structures, thereby reducing the risk of xerostomia and dysphagia [50].

The prescribed radiation dose for HNC varies based on factors such as tumor size, location, histopathology, and treatment intent. In standard fractionation schedules for HNC, patients typically receive 2 Gy per session, administered five times weekly, until reaching a cumulative dose of 60 to 70 Gy [32]. Radiation-related side effects are strongly influenced by both the total dose and the amount delivered per fraction. For instance, in the study conducted by Tsair-Fwu Lee [37], high-risk regions received a cumulative dose of 70 Gy, with each fraction measuring 2.12 Gy. The findings demonstrated that keeping the average dose to the opposite-side salivary glands below 20 Gy markedly decreased the risk of developing xerostomia.

On the other hand, the research of Asghar Mesbahi [17] used a total dose of 72 Gy with 2 Gy per fraction and showed that IMRT can reduce NTCP from 100% (in 3DCRT) to 0.2%. Evidence indicates that increasing the dose per fraction above 2 Gy is associated with a higher risk of both acute and late complications. This was further confirmed in the studies by Ming Chao [39] and Pratik Samant [52], where fractional doses of 2.2 Gy and 2 Gy, respectively, were associated with a higher incidence of xerostomia. The reason for this is that higher doses result in more severe damage to the salivary glands, reducing their functionality. In the study by Pratik Samant [52], reducing the mean dose to the parotid glands significantly lowered the risk of xerostomia. This highlights the importance of dose-volume constraints in treatment planning. The study also showed that, according to Derek K. Smith [42], high doses (>60 Gy) cause irreversible damage to the

salivary glands due to the destruction of the stem cells in the glands and their low regenerative capacity. Mean dose (Dmean) and V15Gy were found to be the best predictors of xerostomia in the study by Panayiotis Mavroidis [58], with AUC values between 0.68 and 0.70.

For dysphagia, Julian Roers [53] reported a total dose of 24-54 Gy with fractional doses of 1.8-3 Gy in patients with lymphoma. Similarly, W. Uijterlinde [54] used a total dose of 66 Gy with a fractional dose of 2.75 Gy for NSCLC patients. Elahe Fathipour [8] also used a total dose of 66 Gy with a fractional dose of approximately 2 Gy for CE. In the study by Jian Zhu [50], doses of 30 to 60 Gy with a fraction size of 2 Gy were used for HNC patients. In another work by Jose Belderbos [59], the comparison of higher doses exceeding 70 Gy delivered by hypofractionated and conventional regimens is presented, showing the higher incidence of dysphagia with higher doses. Comparing the above studies, it can be stated that the increase in fractional dose above 2.75 Gy, as in W. Uijterlinde [54], increases the possibility of dysphagia. This is in agreement with Julian Roers [41], where lower doses were associated with reduced NTCP for dysphagia. In addition, Jose Belderbos [59] showed that hypofractionated doses (5 Gy per fraction) significantly increased the incidence of acute dysphagia.

4.4. LKB model parameters (TD50, m, n)

In the LKB model, the key parameters influencing NTCP include TD50, which represents the tolerance dose for a 50% complication rate, m, which describes the slope of the dose–response curve, and n, which characterizes the volume effect. TD50 is the total dose to the organ that is expected to cause complications in 50% of the cases. It is this slope of the dose-response curve that defines the standard deviation around TD50. The parameter n reflects the volume effect [60]. It has been stated that the volume effect is the relationship between radiation-induced damage in healthy tissue and the volume of the irradiated tissue [61].

Morphologically, a tissue can be expressed as either a series-parallel structure or a combination of the two [62]. Here, the FSUs (Functional Subunit) of the normal organ function relatively independently, meaning that damage to a small area does not affect the entire organ. For severe functional damage to occur, a critical proportion of Functional Subunits (FSUs) must be inactivated [50]. In parallel organs, such as the lungs and parotid glands, damage to a small volume can often be tolerated, whereas high-dose exposure to larger volumes leads to significant functional loss. Parallel organs, such as the lungs and parotid glands, generally have an n value close to 1 [60].

They can also be organized as a chain, with FSUs connected in series to form functional units. In contrast, in such structures, any loss of even a minimal number of vital cells in an FSU leads directly to loss of function of the entire organ. The volume effect is minimal or almost nonexistent for chain organs such as the spinal cord, intestine, and esophagus [63]. For serial organs, the value of n approaches zero, reflecting their high sensitivity to damage in small volumes. By contrast, parallel organs such as the parotid glands have an n value close to 1, and their high radiosensitivity makes them particularly vulnerable to irreversible damage when mean doses exceed 20 Gy.

However, this can be avoided by preserving at least one parotid gland that receives less than the average dose of 20 Gy or both glands that receive less than 25 Gy during irradiation. Evidence, although sparse compared with that for the parotid glands, suggests that maintaining mean doses of no more than 35 Gy to the submandibular glands may reduce xerostomia symptoms [24]. Radiation-induced damage to salivary gland stem cells results in fibrosis, decreased saliva production, and changes in salivary composition [64, 65].

The study by Hubert Szymon Gabryś [19] presented TD50 values of 10.7-13.6 Gy and m = 0.61 for grade 1+ xerostomia at 3 months (short-term). The significance of the TD50 value is that 50% of the population studied would experience xerostomia at this level at an average dose in this range, demonstrating that even at low doses, the salivary glands are extremely sensitive. This means that low doses of radiation strongly affected salivary gland function. The reason for such a low TD50 is the primary and severe damage to the salivary cells. They do not have an immediate regenerative capacity. In such cases, a higher slope (m close to 1) would mean

that the tissue is more sensitive to dose differences, and small differences in dose will give different responses. This heightened sensitivity highlights the necessity of maintaining a continuous effort to combat this side effect, employing methods like IMRT to lessen the radiation exposure to the salivary glands and subsequently reduce the complication. Furthermore, TD50 = 43.9 Gy and m = 0.48 for 12 months after treatment were reported by Tsair-Fwu Lee [37].

The increasing value of TD50 compared to short-term (3 months) values implies that salivary cells regenerate and regain function after exposure to radiation therapy. This restoration occurs due to cell regrowth, local increase in blood perfusion, and decrease in fibrosis. These results show that this enhancement of salivary gland damage caused by radiation therapy decreases over time and eventually allows for partial functional recovery. The value m=0.48 indicates a lower slope than the Gabryś study [19], which means that the examined tissue is relatively less sensitive to dose variation. Thus, the lower the value of m, the smaller is the effect of a small dose variation on the tissue response. According to the study by Ming Chao [39], the full LKB model had a reported TD50of 27 Gy, which is lower than other models. This indicates that the LKB model provided a more accurate fit to dose–response data, capturing variations in dose distribution and predicting complication risk with greater sensitivity compared to simpler statistical models. However, the Mean Dose model predicted lower sensitivity because it depends on the mean radiation dose to the whole gland and ignores dose distributions from regions within the gland. The comparison between the Full LKB model and the Mean Dose results is intended to show that although the LKB considers doses distributed throughout the salivary gland volume, it is more accurate in predicting structural sensitivity and is more important at lower doses, where the probability of complications is higher. For example, Ming Chao [39] validated that the full LKB model yielded a lower TD50 (27 Gy) compared to the mean dose, which predicted greater sensitivity.

Among the dysphagia studies, Julian Roers [53] reported the highest TD50 value (77.5 Gy) for dysphagia alone, suggesting that esophageal tissue is quite tolerant to high doses. The steep slope of the response curve (m = 0.95) in this study reflects higher dose sensitivity. By contrast, Uijterlinde [54] reported much lower sensitivity (m = 0.03) in esophageal tissue, which may be explained by anatomical differences between cervical and thoracic esophagus as well as patient cohort heterogeneity. In her research, Elahe Fathipour [8] presents the estimate of TD50 concerning the induction of swallowing difficulties by radiation therapy in HNC as 47 Gy, indicating that cervical esophageal tissue is much more sensitive than thoracic esophageal tissue. Jian Zhu [66] reported the respective values of TD50 and m for predicting acute dysphagia as 60 Gy and 0.4, suggesting that there is a relatively moderate sensitivity of esophageal tissue to radiation doses and effects. The work of Olivier Chapet [57] used the RS method, which has a higher volume sensitivity than the LKB model. The parameters reported for the esophagus in this study include: n=0.05 and TD50=68 Gy.

In several studies, comparisons of these models show that the TD50 and m values vary according to target regions, types of radiation therapy techniques, and additional treatment conditions such as the presence of chemotherapy. The study by Julian Roers [53], which reported a higher value for both TD50 and m parameters, highlighted the importance of modern techniques such as IMRT to reduce dose exposure to the esophagus, while Elahe Fathipour [8] showed that cervical esophageal tissue has a higher sensitivity to radiation dose. Jian Zhu [66] particularly emphasized the tissue sensitivity at intermediate doses, which played an important role in predicting acute dysphagia.

Across included studies, LKB models reported TD50 values ranging from 27 to 44 Gy for salivary glands, indicating a high sensitivity of these tissues to relatively low doses. For instance, a TD50 of 27 Gy (Full LKB model) implies that a larger proportion of patients may experience complications even at lower dose levels. The m values, ranging from 0.48 to 0.61, reflect the slope of the dose-response curve, with lower m values (e.g., 0.48 in Lee *et al.* [37]) indicating a flatter slope, meaning small dose variations produce less differential tissue response. The n values were generally near 1, consistent with the parallel structure of salivary glands.

Comparatively, RS models showed greater sensitivity to volume effects, especially for smaller irradiated volumes, while machine learning

approaches integrating dosimetric and clinical features achieved AUCs up to 0.90, demonstrating superior predictive performance. This quantitative synthesis emphasizes not only the predictive capacity of classical NTCP models but also the potential for advanced AI-driven models to enhance individualized toxicity prediction.

4.5. Radiation Modality

The method and technique of radiation therapy influence the dose distribution and the incidence of complications. Studies by Pratik Samant [52] and Hubert Szymon Gabryś [19] indicate that IMRT has a high degree of ability to modulate the intensity of the beam, resulting in uniform dose distribution to the tumor with minimal damage to adjacent healthy tissues. 3DCRT is an improvement over earlier methods, but it does not have the same level of sophistication as IMRT in the limited irradiation of radiosensitive tissues (such as the salivary glands). Tomotherapy combines imaging and delivery of radiation therapy, but it is less capable of precise dose distribution than IMRT. Both Pratik Samant [52] and Hubert Szymon Gabryś [19] state that IMRT achieves greater precision in dose distribution than 3DCRT and tomotherapy, thereby reducing the risk of complications. On the other hand, Asghar Mesbahi [17] mentions the major shortcomings of 3DCRT in terms of minimizing the dose risk to healthy tissues and notes an increased risk of complications due to the ineffectiveness of this method in sparing normal tissues from radiation.

Nevertheless, Mesbahi [17] found that IMRT reduces NTCP overall, mainly due to better adaptation of the dose distribution to normal tissues and lower radiation exposure. The decrease in NTCP with IMRT is accompanied by an increase in patients' quality of life after treatment.

This study by Takahiro Kanehira [20] also evaluated more advanced techniques such as VMAT (Volumetric Modulated Arc Therapy), which has been shown to align the delivered dose with the planned dose, thus minimizing the difference between the two. The planned dose is determined by specialized software based on the characteristics of the tumor and the patient, while during treatment delivery, it will vary to some extent due to physical factors such as the patient's movement.

4.6. Follow-up

Patients receiving head and neck radiation therapy may experience xerostomia, which may be acute or chronic and may vary in onset and duration from patient to patient. Acute xerostomia usually begins during or shortly after the initiation of radiation therapy. Studies have shown that almost all patients experience some degree of xerostomia within six months after radiation therapy, often graded in terms of severity (from mild to severe) using established scoring systems [67, 68]. In contrast, chronic xerostomia persists long after the completion of radiation therapy. While the patient may experience a gradual return of salivary gland function over time, other patients may find that their symptoms remain completely unresolved, resulting in a dry mouth problem that persists for many years [57]. This chronic entity is most often due to irreversible damage to the salivary glands from radiation. Chronic xerostomia can cause problems with swallowing, speaking, and oral hygiene for a long time [69].

Xerostomia may present acutely during radiotherapy or persist as a chronic condition requiring long-term management. The follow-up periods in xerostomia studies vary. For example, in the study by Hubert Szymon Gabryś [19], patients were followed for up to 12 months, and a gradual decrease in the incidence of G2+ xerostomia was observed; furthermore, Tsair-FwuLee [37] showed that complications decreased within 12 months after treatment, with longer follow-up needed to detect late effects. According to a long-term evaluation by Tim Dijkema [15], recovery of salivary gland function may continue for approximately 24 months, although it is not complete. A study by Pratik Samant [52] found that a six-month follow-up was sufficient to observe the early appearance of late complications such as xerostomia. Longer follow-up may provide a clearer picture of the recovery path of salivary gland function; therefore, studies with longer follow-up will provide comprehensive data on their recovery. In contrast, Panayiotis Mavroidis [38] studied the one-month follow-up because of the early onset of acute complications, while the three-month and six-month

follow-ups were performed to provide insight into the recovery of glandular function.

4.7. Persistence of Xerostomia and Dysphagia

4.7.1. Xerostomia

Radiation-induced xerostomia may be temporary or permanent depending on the extent of salivary gland damage, leading to complications such as impaired swallowing, speech difficulties, dental problems, and oral infections [70, 71]. Supportive management includes hydration, dietary modification, saliva substitutes, and humidification [70].

4.7.2. Dysphagia

Chronic dysphagia, resulting from fibrosis and neuropathy of swallowing muscles, can severely affect nutrition and quality of life. In some cases, patients require long-term dietary adjustments or gastrostomy feeding [45, 70, 72]. Speech therapy and continuous follow-up are essential to improve functional outcomes [45, 50].

Comparative analysis indicates that while the LKB model provides reliable predictions for xerostomia, alternative RS and machine learning-based models may offer superior accuracy in certain contexts, particularly when accounting for complex dosimetric and patient-specific factors. Heterogeneity among studies, including differences in sample size, dose fractionation, and endpoint definitions, limits generalizability and underscores the need for standardized protocols. Integrating NTCP modeling into clinical practice supports optimized treatment planning, balancing tumor control with minimization of normal tissue toxicity, ultimately improving patient outcomes.

4.7.3. Strengths and Limitations

This literature review addresses the gaps in radiobiological modeling for xerostomia, dysphagia, and esophagitis complications during head-and-neck radiotherapy. One of the main strengths is the methodical search and review of studies, focusing on the LKB model and NTCP prediction studies. The review's clinical applicability is widespread since multiple complications are considered, unlike other reviews that center on a single endpoint. On the other hand, some limitations need to be highlighted. The diversity in the studies used, especially in terms of patients, treatment methods (such as IMRT, VMAT), and the endpoints reported, creates difficulties in directly comparing the findings. Also, the modeling for esophagitis lacked sufficient data, weakening the arguments in that section. While these limitations do not invalidate the results, they indeed affect their weight, and there is a need for further research with uniform methods.

5. Conclusion

In conclusion, radiation therapy for head and neck cancer inevitably affects normal tissues, leading to common complications such as xerostomia and dysphagia, which significantly impair quality of life. Dose, fractionation, and the choice of radiation delivery technique (e.g., IMRT, VMAT) are critical factors in mitigating these side effects. Predictive models, including LKB, RS, and clustering-based approaches, provide valuable tools for estimating the likelihood of toxicity and supporting individualized treatment planning. Evidence indicates that careful management of dose-volume parameters, particularly to salivary glands and pharyngeal constrictors, can reduce the incidence and severity of these complications.

Future research should focus on integrating advanced computational methods, such as AI-driven and radiomics-based models, along with patient-specific biomarkers, to enhance precision in toxicity prediction. Such hybrid approaches can facilitate adaptive radiotherapy, optimize therapeutic outcomes, and ultimately improve the long-term quality of life of patients surviving head and neck cancer.

Acknowledgment

This study was supported by the Lorestan University of Medical Sciences (Grant Number: 1397-1-99-4215).

References

1- Oladejo Olaleye, "Head and neck cancers: epidemiology, diagnosis and treatments." *Journal of Global Medicine,* Vol. 3 (No. S1), p. e121, 12/30 (2023).

2- Mahesh Pavan Kontheti, Upajna Vamaraju, Navya Deepika Burreddy, and Rushi Naidu Tarra, "A PHARMACOLOGICAL REVIEW ON HEAD AND NECK CANCER." (2024).

3- Pratik Samant *et al.*, "Machine learning for normal tissue complication probability prediction: Predictive power with versatility and easy implementation." *Clinical and Translational Radiation Oncology,* Vol. 39p. 100595, 2023/03/01/ (2023).

4- Mostafa alizade-harakiyan, Amir Ghasemi Jangjoo, Behnam Nasiri, Tohid Jafari-Koshki, Murat Okutan, and Asghar Mesbahi, "Radiobiological Modeling of Acute Esophagitis Following Radiotherapy of Thorax and Head-Neck Tumors: A Comparison of Lyman Kutcher Burman with Equivalent Uniform Dose-Based Models." *Iranian Journal of Medical Physics,* Vol. 17 (No. 4), pp. 225–34, (2020).

5- Julian Roers *et al.*, "Impact of Modern Low Dose Involved Site Radiation Therapy on Normal Tissue Toxicity in Cervicothoracic Non-Hodgkin Lymphomas: A Biophysical Study." *Cancers,* Vol. 15 (No. 24), p. 5712, (2023).

6- T. Kanehira, S. van Kranen, T. Jansen, O. Hamming-Vrieze, A. Al-Mamgani, and J. J. Sonke, "Comparisons of normal tissue complication probability models derived from planned and delivered dose for head and neck cancer patients." (in eng), *Radiother Oncol,* Vol. 164pp. 209–15, Nov (2021).

7- D. K. Smith, H. Clark, A. Hovan, and J. Wu, "Neural network and spline-based regression for the prediction of salivary hypofunction in patients undergoing radiation therapy." (in eng), *Radiat Oncol,* Vol. 18 (No. 1), p. 77, May 8 (2023).

8- Elahe Fathipour, Mohammad Amin Mosleh-Shirazi, Mansour Ansari, Mohammad Mohammadianpanah, Mohammad Reza Sasani, and Pyman Jafari, "A prospective radiobiological study of acute esophagitis and swallowing dysfunction in head-and-neck radiotherapy." *Iranian Journal of Medical Physics,* Vol. 15 (No. Special Issue-12th. Iranian Congress of Medical Physics), pp. 59–59, (2018).

9- T. M. Huynh *et al.*, "Radiation-induced long-term dysphagia in survivors of head and neck cancer and association with dose-volume parameters." (in eng), *Radiother Oncol,* Vol. 190p. 110044, Jan (2024).

10- L. Van den Bosch *et al.*, "Key challenges in normal tissue complication probability model development and validation: towards a comprehensive strategy." (in eng), *Radiother Oncol,* Vol. 148pp. 151–56, Jul (2020).

11- Mostafa Alizade-Harakiyan, Amir Ghasemi Jangjoo, Tohid Jafari-Koshki, Ali Fatemi, and Asghar Mesbahi, "Radiobiological modeling of acute esophagitis after radiation therapy of head, neck, and thorax tumors: The influence of chemo-radiation." *Journal of Cancer Research and Therapeutics,* Vol. 18 (No. 6), pp. 1706–15, (2022).

12- A. Chaikh *et al.*, "Construction des modèles radiobiologiques de type TCP (tumor control probability) et NTCP (normal tissue complication probability) : de la dose à la prédiction des effets cliniques." *Cancer/Radiothérapie,* Vol. 24 (No. 3), pp. 247–57, 2020/06/01/ (2020).

13- Giuseppe Palma, Serena Monti, Manuel Conson, Roberto Pacelli, and Laura Cella, "Normal tissue complication probability (NTCP) models for modern radiation therapy." in *Seminars in oncology*, (2019), Vol. 46 (No. 3): *Elsevier*, pp. 210–18.

14- BA Mackenzie Hilton, "J BI Critical appraisal checklist for systematic reviews and research syntheses." *The Journal of the Canadian Health Libraries Association= Journal de l'Association des Bibliothèques de la Santé du Canada,* Vol. 45 (No. 3), pp. 180–83, (2024).

15- Tim Dijkema *et al.*, "Parotid gland function after radiotherapy: the combined Michigan and Utrecht experience." *International Journal of Radiation Oncology* Biology* Physics,* Vol. 78 (No. 2), pp. 449–53, (2010).

16- X. Wang and A. Eisbruch, "IMRT for head and neck cancer: reducing xerostomia and dysphagia." (in eng), *J Radiat Res,* Vol. 57 Suppl 1 (No. Suppl 1), pp. i69–i75, Aug (2016).

17- Asghar Mesbahi, Naser Rasouli, Behnam Nasiri Motlagh, and Mohammad Mohammadzadeh, "Radiobiological model-based comparison of three-dimensional conformal and intensity-modulated radiation therapy plans for nasopharyngeal carcinoma." *Iranian Journal of Medical Physics/Majallah-I Fīzīk-I Pizishkī-i Īrān,* Vol. 14 (No. 4), (2017).

18- Simona Marzi *et al.*, "Analysis of salivary flow and dose–volume modeling of complication incidence in patients with head-and-neck cancer receiving intensity-modulated radiotherapy." *International Journal of Radiation Oncology* Biology* Physics,* Vol. 73 (No. 4), pp. 1252–59, (2009).

19- Hubert Szymon Gabryś, Florian Buettner, Florian Sterzing, Henrik Hauswald, and Mark Bangert, "Parotid gland mean dose as a xerostomia predictor in low-dose domains." *Acta Oncologica,* Vol. 56 (No. 9), pp. 1197–203, (2017).

20- Takahiro Kanehira, Simon van Kranen, Tomas Jansen, Olga Hamming-Vrieze, Abrahim Al-Mamgani, and Jan-Jakob Sonke, "Comparisons of normal tissue complication probability models derived from planned and delivered dose for head and neck cancer patients." *Radiotherapy and Oncology,* Vol. 164pp. 209–15, (2021).

21- Pètra M Braam, Judith M Roesink, Marinus A Moerland, Cornelis PJ Raaijmakers, Maria Schipper, and

Chris HJ Terhaard, "Long-term parotid gland function after radiotherapy." *International Journal of Radiation Oncology* Biology* Physics,* Vol. 62 (No. 3), pp. 659–64, (2005).

22- J. A. Langendijk, P. Doornaert, I. M. Verdonck-de Leeuw, C. R. Leemans, N. K. Aaronson, and B. J. Slotman, "Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy." (in eng), *J Clin Oncol,* Vol. 26 (No. 22), pp. 3770–6, Aug 1 (2008).

23- J. J. Caudell, P. E. Schaner, R. A. Desmond, R. F. Meredith, S. A. Spencer, and J. A. Bonner, "Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck." (in eng), *Int J Radiat Oncol Biol Phys,* Vol. 76 (No. 2), pp. 403–9, Feb 1 (2010).

24- J. O. Deasy, V. Moiseenko, L. Marks, K. S. Chao, J. Nam, and A. Eisbruch, "Radiotherapy dose-volume effects on salivary gland function." (in eng), *Int J Radiat Oncol Biol Phys,* Vol. 76 (No. 3 Suppl), pp. S58–63, Mar 1 (2010).

25- H. P. van der Laan *et al.*, "Swallowing-sparing intensity-modulated radiotherapy for head and neck cancer patients: treatment planning optimization and clinical introduction." (in eng), *Radiother Oncol,* Vol. 107 (No. 3), pp. 282–7, Jun (2013).

26- Kamal M, "Radiotherapy dose reduction in swallowing structures using IMRT." *Oral Oncol,* (2016;62:90–96.).

27- G. Carnaby-Mann, M. A. Crary, I. Schmalfuss, and R. Amdur, ""Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy." (in eng), *Int J Radiat Oncol Biol Phys,* Vol. 83 (No. 1), pp. 210–9, May 1 (2012).

28- Timo M Deist *et al.*, "Machine learning algorithms for outcome prediction in (chemo) radiotherapy: An empirical comparison of classifiers." *Medical physics,* Vol. 45 (No. 7), pp. 3449–59, (2018).

29- J. A. Dean *et al.*, "Normal tissue complication probability (NTCP) modelling using spatial dose metrics and machine learning methods for severe acute oral mucositis resulting from head and neck radiotherapy." (in eng), *Radiother Oncol,* Vol. 120 (No. 1), pp. 21–7, Jul (2016).

30- et al Wong KH, "Deep learning predicts radiotherapy outcomes in head and neck cancer." *Nat Med. ,* (2022;28(5):815–816.).

31- et al. Van Rij CM, "Artificial intelligence for NTCP prediction in head and neck cancer." *Front Oncol.,* (2021;11:634420).

32- A. F. Alfouzan, "Radiation therapy in head and neck cancer." (in eng), *Saudi Med J,* Vol. 42 (No. 3), pp. 247–54, Mar (2021).

33- Z. Wang *et al.*, "Lyman-Kutcher-Burman normal tissue complication probability modeling for radiation-induced esophagitis in non-small cell lung cancer patients receiving proton radiotherapy." (in eng), *Radiother Oncol,* Vol. 146pp. 200–04, May (2020).

34- M. Chen *et al.*, "Predictive performance of different NTCP techniques for radiation-induced esophagitis in NSCLC patients receiving proton radiotherapy." (in eng), *Sci Rep,* Vol. 12 (No. 1), p. 9178, Jun 2 (2022).

35- L. Cella *et al.*, "Complication probability models for radiation-induced heart valvular dysfunction: do heart-lung interactions play a role?" (in eng), *PLoS One,* Vol. 9 (No. 10), p. e111753, (2014).

36- EH Quik *et al.*, "Individual patient information to select patients for different radiation techniques." *European Journal of Cancer,* Vol. 62pp. 18–27, (2016).

37- Tsair-Fwu Lee and Fu-Min Fang, "Quantitative analysis of normal tissue effects in the clinic (QUANTEC) guideline validation using quality of life questionnaire datasets for parotid gland constraints to avoid causing xerostomia during head-and-neck radiotherapy." *Radiotherapy and Oncology,* Vol. 106 (No. 3), pp. 352–58, (2013).

38- Panayiotis Mavroidis *et al.*, "NTCP modeling and dose–volume correlations for acute xerostomia and dry eye after whole brain radiation." *Radiation Oncology,* Vol. 16pp. 1–11, (2021).

39- Ming Chao, Jie Wei, Yeh-Chi Lo, and José A Peñagarícano, "Dose cluster model parameterization of the parotid gland in irradiation of head and neck cancer." *Physical and Engineering Sciences in Medicine,* Vol. 43pp. 143–53, (2020).

40- M. Chao, J. Wei, Y. C. Lo, and J. A. Peñagarícano, "Dose cluster model parameterization of the parotid gland in irradiation of head and neck cancer." (in eng), *Australas Phys Eng Sci Med,* Dec 2 (2019).

41- P. Dirix, S. Nuyts, and W. Van den Bogaert, "Radiation-induced xerostomia in patients with head and neck cancer: a literature review." (in eng), *Cancer,* Vol. 107 (No. 11), pp. 2525–34, Dec 1 (2006).

42- Derek K Smith, Haley Clark, Allan Hovan, and Jonn Wu, "Neural network and spline-based regression for the prediction of salivary hypofunction in patients undergoing radiation therapy." *Radiation Oncology,* Vol. 18 (No. 1), p. 77, (2023).

43- C. Silvain *et al.*, "Treatment and long-term outcome of chronic radiation esophagitis after radiation therapy for head and neck tumors. A report of 13 cases." (in eng), *Dig Dis Sci,* Vol. 38 (No. 5), pp. 927–31, May (1993).

44- I. Brook, "Early side effects of radiation treatment for head and neck cancer." (in eng), *Cancer Radiother,* Vol. 25 (No. 5), pp. 507–13, Jul (2021).

45- Thuy-Tien Maria Huynh *et al.*, "Radiation-induced long-term dysphagia in survivors of head and neck cancer

and association with dose-volume parameters." *Radiotherapy and Oncology,* Vol. 190(2024).

46- Susyana Tamin, Marlinda Adham, Elvie Z Rachmawati, Sabda Ardiantara, and Eka D Safitri, "Salivary Gland Dysfunction and Dysphagia in Post-Chemoradiotherapy Head and Neck Malignancy Patients." *eJournal Kedokteran Indonesia,* pp. 220–9, (2021).

47- S. Mercadante *et al.*, "Prevalence of oral mucositis, dry mouth, and dysphagia in advanced cancer patients." (in eng), *Support Care Cancer,* Vol. 23 (No. 11), pp. 3249–55, Nov (2015).

48- Lisa Van den Bosch, "Risk-based treatment optimisation to reduce radiation-induced toxicity in head and neck cancer patients." (2022).

49- Cochrane Haematology Group *et al.*, "Prognostic models for radiation-induced complications after radiotherapy in head and neck cancer patients." *Cochrane Database of Systematic Reviews,* Vol. 2021 (No. 5), (1996).

50- Christopher Nutting *et al.*, "Dysphagia-optimised intensity-modulated radiotherapy versus standard intensity-modulated radiotherapy in patients with head and neck cancer (DARS): a phase 3, multicentre, randomised, controlled trial." *The Lancet Oncology,* Vol. 24 (No. 8), pp. 868–80, (2023).

51- R. Govender, N. Gilbody, G. Simson, R. Haag, C. Robertson, and E. Stuart, "Post-Radiotherapy Dysphagia in Head and Neck Cancer: Current Management by Speech-Language Pathologists." (in eng), *Curr Treat Options Oncol,* Vol. 25 (No. 6), pp. 703–18, Jun (2024).

52- Pratik Samant *et al.*, "Machine learning for normal tissue complication probability prediction: predictive power with versatility and easy implementation." *Clinical and Translational Radiation Oncology,* Vol. 39p. 100595, (2023).

53- Julian Roers *et al.*, "Impact of Modern Low Dose Involved Site Radiation Therapy on Normal Tissue Toxicity in Cervicothoracic Non-Hodgkin Lymphomas: A Biophysical Study." *Cancers,* Vol. 15 (No. 24), p. 5712, (2023).

54- Wilhelmina Ida Uijterlinde, "Prediction of toxicity in concurrent chemoradiation for non-small cell lung cancer." *Radiotherapy and Oncology,* Vol. 110pp. 488–92, (2014).

55- Britta Warwas *et al.*, "Risk factors for xerostomia following radiotherapy of head-and-neck cancers." *Anticancer Research,* Vol. 42 (No. 5), pp. 2657–63, (2022).

56- P. Dirix, S. Nuyts, V. Vander Poorten, P. Delaere, and W. Van den Bogaert, "The influence of xerostomia after radiotherapy on quality of life: results of a questionnaire in head and neck cancer." (in eng), *Support Care Cancer,* Vol. 16 (No. 2), pp. 171–9, Feb (2008).

57- Olivier Chapet, Feng-Ming Kong, Julia S Lee, James A Hayman, and Randall K Ten Haken, "Normal tissue complication probability modeling for acute esophagitis in patients treated with conformal radiation therapy for non-small cell lung cancer." *Radiotherapy and Oncology,* Vol. 77 (No. 2), pp. 176–81, (2005).

58- P Mavroidis *et al.*, "NTCP Modeling of Patient Reported Xerostomia after De-Intensified Chemoradiotherapy for HPV Associated Oropharynx Cancer." *International Journal of Radiation Oncology, Biology, Physics,* Vol. 105 (No. 1), p. S4, (2019).

59- J. Belderbos, W. Heemsbergen, M. Hoogeman, K. Pengel, M. Rossi, and J. Lebesque, "Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy." (in eng), *Radiother Oncol,* Vol. 75 (No. 2), pp. 157–64, May (2005).

60- V. A. Semenenko and X. A. Li, "Lyman-Kutcher-Burman NTCP model parameters for radiation pneumonitis and xerostomia based on combined analysis of published clinical data." (in eng), *Phys Med Biol,* Vol. 53 (No. 3), pp. 737–55, Feb 7 (2008).

61- L. H. Gray, "Actions of radiations on living cell, 1946 and after the second Douglas Lae memorial lecture." (in eng), *Br J Radiol,* Vol. 25 (No. 293), pp. 235–44, Mar (1952).

62- P. Källman, A. Agren, and A. Brahme, "Tumour and normal tissue responses to fractionated non-uniform dose delivery." (in eng), *Int J Radiat Biol,* Vol. 62 (No. 2), pp. 249–62, Aug (1992).

63- X. Allen Li *et al.*, "The use and QA of biologically related models for treatment planning: short report of the TG-166 of the therapy physics committee of the AAPM." (in eng), *Med Phys,* Vol. 39 (No. 3), pp. 1386–409, Mar (2012).

64- Rjhm Steenbakkers *et al.*, "Parotid Gland Stem Cell Sparing Radiation Therapy for Patients With Head and Neck Cancer: A Double-Blind Randomized Controlled Trial." (in eng), *Int J Radiat Oncol Biol Phys,* Vol. 112 (No. 2), pp. 306–16, Feb 1 (2022).

65- M. Guerin, A. Orazakai, K. S. Cross, and S. Beatty, "Endogenous endophthalmitis following ipsilateral carotid endarterectomy." (in eng), *Ir J Med Sci,* Vol. 177 (No. 1), pp. 73–4, Mar (2008).

66- Jian Zhu *et al.*, "Analysis of acute radiation-induced esophagitis in non-small-cell lung cancer patients using the Lyman NTCP model." *Radiotherapy and Oncology,* Vol. 97 (No. 3), pp. 449–54, (2010).

67- Yanxia Liu *et al.*, "Early prediction of acute xerostomia during radiation therapy for nasopharyngeal cancer based on delta radiomics from CT images." *Quantitative Imaging in Medicine and Surgery,* Vol. 9 (No. 7), pp. 1288–302, (2019).

68- D. Rades *et al.*, "Prognostic Factors for Complete Recovery From Xerostomia After Radiotherapy of Head-

and-Neck Cancers." (in eng), *In Vivo,* Vol. 36 (No. 4), pp. 1795–800, Jul–Aug (2022).

69- I. Brook, "Late side effects of radiation treatment for head and neck cancer." (in eng), *Radiat Oncol J,* Vol. 38 (No. 2), pp. 84–92, Jun (2020).

70- K. A. Hutcheson *et al.*, "Late dysphagia after radiotherapy-based treatment of head and neck cancer." (in eng), *Cancer,* Vol. 118 (No. 23), pp. 5793–9, Dec 1 (2012).

71- NHS, "Swallowing problems (dysphagia) from

radiotherapy or chemoradiotherapy." (2022).

72- P. Strojan *et al.*, "Treatment of late sequelae after radiotherapy for head and neck cancer." (in eng), *Cancer Treat Rev,* Vol. 59pp. 79–92, Sep (2017).