

A comparative study between the effect of radio-chemotherapy versus surgery with or without postoperative radiotherapy on advanced stage hypopharyngeal carcinoma (stage III and IV); review of literature

Abstract

Background: The improvement of clinical outcomes for patients with hypopharyngeal squamous cell carcinoma (SCC) has been particularly challenging for head and neck surgeons and oncologists. Chemoradiotherapy (CRT) has been used for patients with advanced hypopharyngeal cancer with the aim of preserving the larynx. The reasons for the un-favorable prognosis of hypopharyngeal cancers are the strong tendency for extensive sub-mucosal spread, the early occurrence of regional lymphatic involvement, and the relatively high rate of distant spread.

Aim: This study was conducted to collect the recent data about the different modalities of management of advanced stage hypopharyngeal carcinoma (stage III and IV), and systematically review the outcomes of each modality either alone or in combination and compare their efficacy.

Methods: Search of published medical articles from 2001 till 2018, on management of advanced hypopharyngeal carcinoma either by radio- chemotherapy versus surgery alone or in combination with postoperative radiotherapy in Medline, Embase, Elsevier. Twenty-one articles fulfilled the inclusion criteria and were included in our study.

Results: Overall survival, regarding surgery group was reported in 8 studies with total 1657 patients achieved overall survival (46.23%); While in CRT group, it was reported in 18 studies with total 2995 patients achieved overall survival (43%). Comparative study between the 2 groups revealed decrease in overall survival rate; in CRT group; compared to surgery group; with significant statistical difference ($p=0.019$).

Conclusion: The treatment approach had a significant impact on overall survival and recurrence rate, as described in other series. Given the equivalence between these two strategies suggested in several series, definitive CRT seems to be an advantageous option as it improves organ preservation and, consequently, the functional outcome. Recent developments in chemo-radiation treatment techniques could hopefully increase tumor management and survival rates.

Keywords: advanced hypopharyngeal carcinoma management, treatment of hypopharyngeal carcinoma stage III and IV, radio-chemotherapy in advanced hypopharyngeal carcinoma management, surgery in advanced hypopharyngeal carcinoma management, radio-chemotherapy versus surgery in hypopharyngeal carcinoma, pyriform sinus, post cricoid, posterior wall carcinoma management

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Abbreviations: CRT, chemoradiotherapy; SCC, squamous cell carcinoma; HSCC, hypopharyngeal squamous cell carcinoma; QOL, quality of life

Introduction

Hypopharyngeal cancer is a rare disease representing about 0.5% of all human malignancies with an incidence of less than 1 per 100 000 populations and constituting only 3-5% of all head and neck cancers. Hypopharyngeal cancers are often at an advanced stage at diagnosis and are associated with a poor prognosis.¹⁻³ Therefore, the improvement of clinical outcomes for patients with hypopharyngeal SCC has been particularly challenging for head and neck surgeons

and oncologists. CRT has been used for patients with advanced hypopharyngeal cancer with the aim of preserving the larynx. The reasons for the un-favorable prognosis of hypopharyngeal cancers are the strong tendency for extensive sub-mucosal spread, the early occurrence of regional lymphatic involvement, and the relatively high rate of distant spread.⁴

In the 1970s and 1980s, surgical resection followed by radiotherapy has been the standard treatment for advanced hypopharyngeal squamous cell carcinoma (HSCC).⁵ This radical approach of treatment, lead to the loss of natural speech function and impairment of swallowing ability with a consequent negative impact on the quality of life, and low cure rates, reported 5-year

survival between 20.0% and 50.0%.⁶ However, since the early 1990s, chemo- radiation (CRT) has become a valuable alternative treatment option. Due to organ preservation, it has been suggested that CRT is followed by a better long-term quality of life (QOL) than after total laryngopharyngectomy, with similar survival.⁷

The aim: Systematically review the outcomes of surgery versus chemo-radiotherapy and compare their efficacy in advanced stage hypopharyngeal carcinoma (stage III and IV).

Methods

Target determination: Our target is to compare the effect of radio-chemotherapy versus surgery alone or in combination with postoperative radiotherapy in advanced hypopharyngeal carcinoma (stage III and IV).

Identification and location of articles: The study included the published medical articles on management of advanced hypopharyngeal carcinoma either by radio- chemotherapy versus surgery alone or in combination with postoperative radiotherapy through searching, Medline, Embase, Elsevier.

Screening and evaluation: The screening form of articles which was yielded by the search engine after blinding the author name and journal name.

Screen form of the articles

Irrelevant articles: articles that missed one or more from the above keywords.

Relevant articles: articles, which contain one or more from the above keywords, and after exclusion of repeated articles.

Included articles: These are the articles, which fulfilled the following inclusion criteria:

- Articles in English language.
- Number of patients reported.
- Patients diagnosed as having advanced hypopharyngeal carcinoma (stage III and IV).
- Used either single or multimodality (radio-chemotherapy – surgery or combination of them).
- The outcome is reported.
- Papers published in the last 10 years.

Excluded articles: Articles which missed one or more of the above mentioned inclusion criteria.

Data collection

The data collected from the included articles included:

- Type of study (prospective, retrospective, systematic review, meta-analysis or randomized control).
- Number of patients treated with radio-chemotherapy.
- Number of patients treated with surgery with or without postoperative radiotherapy
- Outcomes and results.

Statistical analysis: Data entry, processing and statistical analysis was carried out using MedCalc ver. 15.8 (MedCalc, Ostend, Belgium). A statistical-analysis was performed to calculate direct estimates of treatment effect for each treatment modality. According to heterogeneity of treatment effect across trials using the I statistics; a fixed-effect model ($P \geq 0.1$) or random-effects model ($P < 0.1$) was used. Generally, P-values less than 0.05 (5%) was considered to be statistically significant.

P-value: level of significance

$P > 0.05$: Non-significant (NS).

$P < 0.05$: Significant (S).

$P < 0.01$: Highly significant (HS).

Results

After applying our keywords, we found 650 published articles, and after removal of duplication we found that we had 160 articles and 450 articles were excluded based on title. Then 119 articles could not be accessed or obtained as a full text, 20 articles were excluded as follows; 10 articles were review and case reports and 3 articles did not include the functional outcome, 7 articles did not correspond to the intended plan of management. Finally, 21 studies met our inclusion criteria. The demographic characteristics and clinical data in all 21 studies are shown in the following tables and figures. The included articles as shown in Table 1 are published between 2001 and 2018. Regarding the type of therapeutic interventions; 2 studies used surgery technique only; 13 studies used CRT technique only, while 6 studies compared both techniques. The total number of patients in all the included studies was 10539 patients; while the biggest study was Shah and his colleagues in 2016¹ as they studied 9106 patients; and the smallest study was by Suzuki G. and his colleagues in 2013² as they studied only 19 patients.

- Regarding surgery group, the total number of patients was (3584) patients in 8 studies.
- Regarding CRT group, the total number of patients was (6955) patients in 19 studies. Data were divided into two groups:
 - Surgery treatment group (Surgery).
 - CRT treatment group (CRT).

Present study was done on 21 studies, which described and compared the 2 different techniques for treatment outcomes; with overall number of patients (N=10539) (Table 2).

- We calculated efficacy for each technique through (overall survival and success rates).
- We calculated safety for each technique through (Local recurrence rate, distant metastatic rate, overall recurrence, and mortality rates).

Favorable treatment outcomes (surgery group) (Table 3):

Regarding surgery group, the overall survival was reported in 8 studies with (1657) of total (3584) Patients achieved overall survival.

Success rate was reported in 7 studies with (192) of total (385) patients achieved full response to surgery. Larynx preservation rate was not reported in any study.

Table 1 Patients and study characteristics in all studies

N	Author	Type of study	No\pts \surgery	No\pts \CRT
1	Juloori 2018	Retrospective	NM	54
2	Nomura 2018	Retrospective	33	NM
3	Chen 2018	Retrospective	133	124
4	Kim 2017	Retrospective	21	39
5	Masuda 2017	Retrospective	23	27
6	Otsuki 2017	Retrospective	NM	50
7	Shah 2016	Retrospective	3199	5907
8	Kim 2016	Retrospective	NM	34
9	Reis 2016	Retrospective	NM	81
10	Van 2015	Retrospective	NM	35
11	Sakashita 2015	Retrospective	NM	30
12	Harris 2015	Retrospective	28	48
13	Suzuki K 2013	Retrospective	NM	79
14	Suzuki G 2013	Retrospective	NM	19
15	Al Mamgani 2012	Retrospective	NM	176
16	Keereweer 2012	prospective	NM	73
17	Krstevska 2010	Retrospective	NM	41
18	Chang 2010	prospective	81	79
19	Iwai 2008	Retrospective	NM	27
20	Clark 2006	Retrospective	66	NM
21	Kim 2001	Retrospective	NM	32

#Studies were arranged according to publication year. NM: not mentioned. CRT: chemo-radiotherapy

Table 2 Summary of different treatment outcomes regarding 2 management modalities

		Surgery+ combined	Combined 2 modalities	CRT + combined
Studies		2+6	6	13+6
patients		3584		6955
OS	Articles	8	6	18
	Patients	1657\3584	9709	2995\6876
SR	Articles	7	5	15
	Patients	192\385	603	436\989
LR	Articles	4	3	6
	Patients	80\243	367	125\313
DM	Articles	4	3	12
	Patients	59\243	367	137\610
OR	Articles	2	2	9
	Patients	47\156	307	198\459
MR	Articles	3	2	8
	Patients	75\222	307	186\544

Table 3 Favorable treatment outcomes in surgery group

N	Author	Favorable outcomes		
		Overall Survival rate	Success rate	Larynx preservation
1	Nomura 2018	27 (82.2%)	32 (95.7%)	NM
2	Chen 2018	71 (53.4%)	63 (47.6%)	NM
3	Kim 2017	12 (59%)	15 (71%)	NM
4	Masuda 2017	13 (57%)	17 (76%)	NM
5	Shah 2016	1475 (46.1%)	NM	NM
6	Harris 2015	19 (66.3%)	15 (53.6%)	NM
7	Chang 2010	15 (19%)	20 (24.2%)	NM
8	Clark 2006	25 (38%)	30 (45%)	NM

Un-favorable treatment outcomes (surgery group) (Table 4):

Regarding surgery group, local recurrence rate was reported in 4 studies with (80) of total (243) patients.

Distant metastatic rate was reported in 4 studies with (59) of total (243) patients.

Overall recurrence rate was reported in 2 studies with (47) of total (165) patients.

Mortality rate was reported in 3 studies with (75) of total (222) patients died out.

Failure rate and complications rate was not reported in any study.

Table 4 Un-favorable treatment outcomes in surgery group

N	Author	Un-favorable outcomes					
		LRR	DMR	ORR	FR	CR	MR
1	Chen 2018	38 (28.2%)	28 (21.2%)	44 (33%)	NM	NM	60 (45.1%)
2	Kim 2017	10 (49.5%)	18 (85.7%)	NM	NM	NM	NM
3	Masuda 2017	4 (17.3%)	5 (21.7%)	3 (13.7%)	NM	NM	13 (56.5%)
4	Clark 2006	28 (42%)	8 (12.1%)	NM	NM	NM	2 (3%)

LRR, local recurrence rate; DMR, distant metastasis rate; ORR, overall recurrence rate; FR, failure rate; CR, complication rate; MR, mortality rate

Favorable treatment outcomes (CRT group) (Table 5):

Regarding CRT group, the overall survival was reported in 18 studies with (2995) of total (6876) Patients achieved overall survival.

A. Success rate was reported in 15 studies with (436) of total (989) patients achieved full response to CRT.

B. Larynx preservation rate was reported in 10 studies with (311) of total (658) patients achieved Larynx preservation.

4. Failure rate was reported in 5 studies with (97) of total (441) of failed patients.

5. Complications rate was reported in 9 studies with (144) of total (486) patients had complications.

6. Mortality rate was reported in 8 studies with (186) of total (544) patients died out.

Comparative analysis of studies included Comparison between Surgery group and CRT group:

We started to compare the 2 groups according to different outcomes; data are shown in the following tables and figures (Table 7). Comparative study between the 2 groups revealed non-significant difference as regards the average number of patients ($p>0.05$) (Table 7). Patients who achieved favorable outcomes were pooled to evaluate efficacy by: The efficacy of each technique was measured by:

Un-favorable treatment outcomes (CRT group) (Table 6):

1. Regarding CRT group, Local recurrence rate was reported in 6 studies with (125) of total (313) patients.

2. Distant metastasis rate was reported in 12 studies with (137) of total (610) patients.

3. Overall recurrence rate was reported in 9 studies with (198) of total (459) patients.

Table 5 Favorable treatment outcomes in CRT group

N	Author	Favorable outcomes		
		Overall Survival rate	Success rate	Larynx preservation
1	JULOORI 2018	23 (43%)	39 (72%)	NM
2	Chen 2018	40 (32.3%)	82 (66.4%)	30 (24.2%)
3	Kim 2017	13 (34%)	13 (34%)	NM
4	Masuda 2017	19 (72%)	21 (76%)	4 (14%)
5	Otsuki 2017	33 (65.3%)	NM	NM
6	Shah 2016	2587 (43.8%)	NM	NM
7	Kim 2016	20 (58.6%)	17 (51%)	22 (64.7%)
8	Reis 2016	24 (29.2%)	10 (12.5%)	NM
9	Van 2015	9 (27%)	13 (36%)	NM
10	Sakashita 2015	26 (87%)	NM	22 (74%)
11	Harris 2015	20 (41.3%)	17 (34.5%)	NM
12	Suzuki K 2013	NM	NM	7 (9%)
13	Suzuki G 2013	10 (50%)	9 (48%)	13 (70%)
14	Al Mamgani 2012	65 (37%)	90 (51%)	141 (80%)
15	Keereweer 2012	28 (38%)	30 (41%)	53 (72.7%)
16	Krstevska 2010	13 (32.8%)	12 (29.3%)	NM
17	Chang 2010	34 (43.1%)	42 (53%)	NM
18	Iwai 2008	17 (63%)	25 (93.3%)	8 (28.1%)
19	Kim 2001	14 (43%)	16 (49.7%)	11 (34.3%)

Table 6 Un-favorable treatment outcomes in CRT group

N	Author	Un-favorable outcomes					
		LRR	DMR	ORR	FR	CR	MR
1	Juloori 2018	12 (22%)	13 (24%)	NM	NM	29 (53.7%)	2 (3.7%)
2	Chen 2018	65 (52.6%)	31 (24.9%)	65 (52.4%)	34 (27.4%)	NM	62 (50%)
3	Kim 2017	14 (35.8%)	18 (46.1%)	NM	NM	NM	NM
4	Masuda 2017	8 (30%)	8 (30%)	8 (30%)	NM	14 (40%)	6 (22.2%)
5	Kim 2016	8 (23.5%)	4 (11.7%)	12 (35.3%)	NM	4 (12%)	NM
6	Reis 2016	NM	20 (25%)	NM	NM	NM	NM
7	Van 2015	18 (50%)	NM	NM	NM	NM	NM
8	Sakashita 2015	NM	5 (17%)	10 (33%)	4 (13%)	1 (3%)	1 (3.3%)
9	Suzuki K 2013	NM	11 (13.9%)	33 (41.7%)	46 (58.3%)	NM	NM
10	Suzuki G 2013	NM	NM	9 (48%)	NM	6 (32%)	6 (30%)
11	Al Mamgani 2012	NM	NM	NM	10 (5.6%)	28 (16%)	98(55.6%)
12	Keereweer 2012	NM	9 (12.3%)	28 (38.3%)	NM	27 (37%)	2 (3%)
13	Krstevska 2010	NM	10 (24.4%)	12 (29.2%)	NM	27 (65.0%)	9 (21%)
14	Iwai 2008	NM	2 (7.6%)	NM	NM	NM	NM
15	Kim 2001	NM	6 (17.6%)	21 (65.9%)	3 (8%)	8 (25%)	NM

Table 7 Comparison between the 2 groups of studies as regards patient numbers using Mann-Whitney's U test

Variable	CRT(19 studies)	Surgery(8 studies)	Mann-Whitney's U test
	Median (IQR)	Median (IQR)	P value
No\patients	48 (32.5 – 79)	49.5 (25.5 – 107)	= 0.852

IQR, inter-quartile range

Risk ratio (RR)

- For achievement of overall survival rate.
- For achievement of success rate.

Favorable treatment outcomes:

Comparative study between the 2 groups revealed; significant decrease in overall survival rate; in CRT group; compared to surgery group; with significant statistical difference (p=0.019) (Table 8).

Comparative study between the 2 groups revealed non-significant

difference as regards success rate (p>0.05) (Figure 1).

CRT vs. surgery

6 studies reported overall survival rate simultaneously, with total number of patients (N=9709).

Statistical-analysis as shown in Table 9 showed that; fixed-effects model showed significant increase in overall survival rate in favor of surgery studies, while and random-effects model showed non-significant difference between the 2 groups (p=0.013, p >0.05 respectively).

Table 8 Comparison between the 2 groups of studies as regards favorable treatment outcomes by Chi square test

Variable	CRT(19 studies) N=6955	Surgery(8 studies) N=3584	P value
Overall Survival rate	2995 (43%) (18 studies)	1657 (46.2%) ^^ (8 studies)	= 0.019**
Success rate	436 (6.2%) (15 studies)	192 (5.3%) ^^ (7 studies)	= 0.0611
Larynx preservation	311 (4.5%) (described in 10 studies)	---	---(can't be assessed)

N=number of patients underwent this procedure. % per column total. ^^ total % < 100% as outcomes was not mentioned in all studies

Table 9 Statistic-analysis of (overall survival rate) achievement on CRT vs surgery usage - Risk Ratio

N	Study	CRT	Surgery	RR	95% CI	Z	P value	Weight (%)	
								Fixed	Random
1	Chen 2018	40/124	71/133	0.60	0.447 to 0.816			2.33	18.82
2	Kim 2017	13/39	12/21	0.58	0.327 to 1.040			0.63	12.73
3	Masuda 2017	19/27	13/23	1.24	0.807 to 1.922			1.12	15.78
4	Shah 2016	2587/5907	1475/3199	0.95	0.906 to 0.996			93.97	22.74
5	Harris 2015	20/48	19/28	0.61	0.403 to 0.935			1.19	16.08
6	Chang 2010	34/79	15/81	2.32	1.378 to 3.919			0.77	13.85
	T (fixed effects)	2713/6224	1605/3485	0.94	0.901 to 0.988	- 2.48	0.013*	100	100
	T (random effects)	2713/6224	1605/3485	0.90	0.662 to 1.231	-	0.518	100	100
						0.64			

T, total; Q test for heterogeneity = 28.18, degree of freedom (DF) = 5, p < 0.001**, I² (inconsistency) = 82.2% and risk ratio (RR) = 0.9

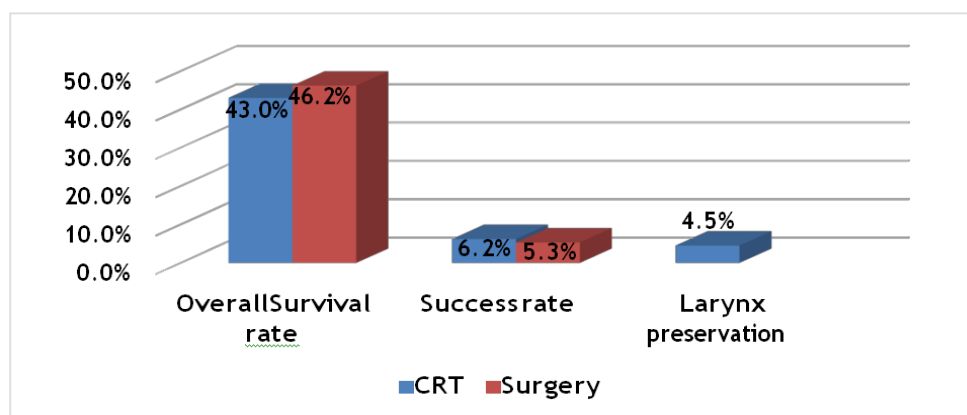


Figure 1 Comparison between the 2 groups of studies as regards favorable treatment outcomes.

I (inconsistency) was 82%; with highly significant Q test for heterogeneity ($p < 0.01$); so random-effects model was chosen to assess efficacy; with overall $RR = 0.9$ and a 95% CI for achievement of (overall survival) ranged from 0.662 to 1.231, with non-significant difference in efficacy in the CRT group compared to surgery group ($p > 0.05$) as shown in Table 9 & Figure 2.

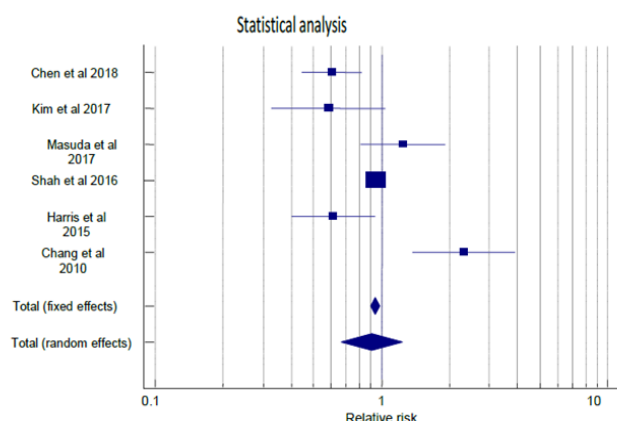


Figure 2 Forest plot of (overall survival rate) achievement on CRT vs surgery usage - Risk Ratio.

Five studies reported success rate simultaneously, with total number of patients ($N = 603$).

Statistical analysis as shown in Table 10; fixed-effects model showed significant increase in success rate in favor of CRT studies, while and random-effects model showed non-significant difference between the 2 groups ($p = 0.01$, $p > 0.05$ respectively).

I (inconsistency) was 85.5%; with highly significant Q test for heterogeneity ($p < 0.01$); so random-effects model was chosen to assess efficacy; with overall $RR = 1.02$ and a 95% CI for achievement of (success rate) ranged from 0.664 to 1.584, with non-significant difference in efficacy in the CRT group compared to surgery group ($p > 0.05$) (Figure 3).

Un-favorable treatment outcomes:

Comparative study between the 2 groups revealed; significant increase in overall recurrence rate; in CRT group; compared to

surgery group; with highly significant statistical difference ($p < 0.01$) (Table 11).

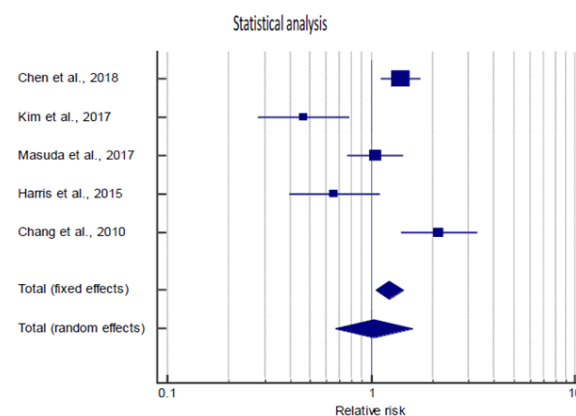


Figure 3 Forest plot of (success rate) achievement on CRT vs. surgery usage - Risk Ratio.

Comparative study between the 2 groups revealed non-significant difference as regards Local recurrence rate, distant metastatic rate, and mortality rates ($p > 0.05$) (Figure 4).

Patients who reached serious adverse events (SAEs) –were pooled to evaluate safety by: Safety of each technique that was measured by:

Risk ratio (RR)

- Local recurrence rate.
- Distant metastatic rate.
- Overall recurrence rate.
- Mortality rate.

We found 3 studies reported local recurrence rate simultaneously, with total number of patients ($N = 367$). Statistical-analysis as shown in Table 12; showed that fixed-effects model showed significant decrease in local recurrence rate in favor of surgery studies, while and random-effects model showed non-significant difference between the 2 groups ($p = 0.001$, $p > 0.05$ respectively).

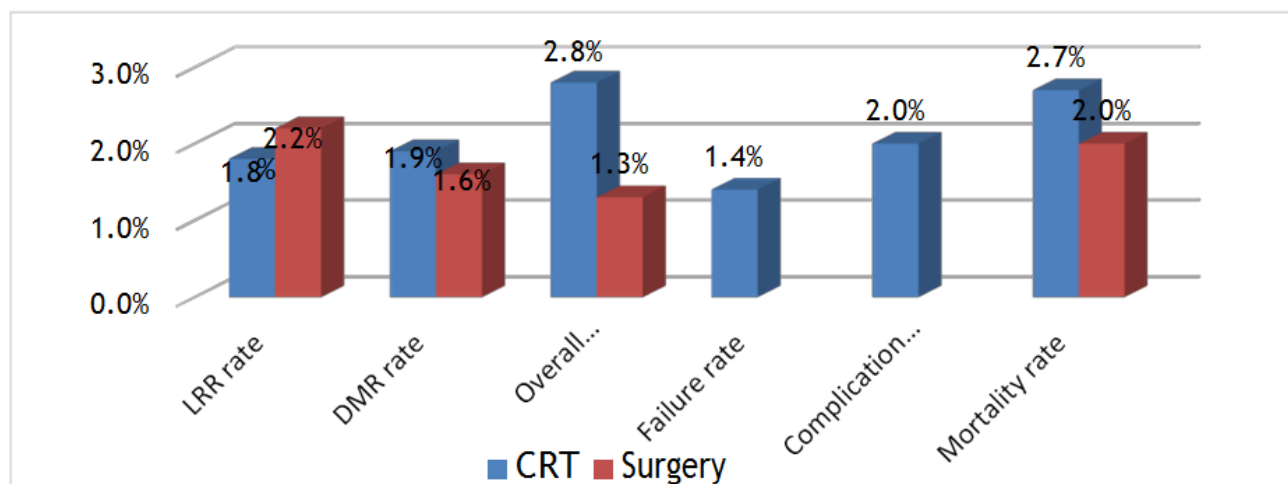


Figure 4 Comparison between the 2 groups of studies as regards un-favorable treatment outcomes.

Table 10 Statistical-analysis of (success rate) achievement on CRT vs. surgery usage - Risk Ratio

N	Study	CRT	Surgery	RR	95% CI	Z	P value	Weight (%)	
								Fixed	Random
1	Chen 2018	82/124	63/133	1.39	1.121 to 1.738			47.71	22.84
2	Kim 2017	13/39	15/21	0.46	0.278 to 0.785			8.47	18.01
3	Masuda 2017	21/27	17/23	1.05	0.767 to 1.443			22.97	21.50
4	Harris 2015	17/48	15/28	0.66	0.395 to 1.106			8.64	18.10
5	Chang 2010	42/79	20/81	2.15	1.396 to 3.320			12.20	19.55
	T (fixed effects)	175/31	130/28	1.22	1.050 to 1.430	2.583	0.01*	100	100
	T (random effects)	7	6	1.02	0.664 to 1.584	0.112	0.911	100	100
		7	6						

Q test for heterogeneity = 27.54, degree of freedom (DF) = 4, $p < 0.001^{**}$, I^2 (inconsistency) = 85.5% and risk ratio (RR) = 1.02

Table 11 Comparison between the 2 groups of studies as regards un-favorable treatment outcomes using Chi square test

Variable	CRT (19 studies) N=6955	Surgery(8 studies) N=3584	P value
LRR	125 (1.8%) (6 studies)	80 (2.2%) ^^ (4 studies)	= 0.125
DMR	137 (1.9%) (12 studies)	59 (1.6%) ^^ (4 studies)	= 0.244
ORR	198 (2.8%) (9 studies)	47 (1.3%) ^^ (2 studies)	< 0.0001**
FR	97 (1.4%) (5 studies)	---	---(can't be assessed)
CR	144 (2%) (9 studies)	---	---(can't be assessed)
MR	186 (2.7%) (8 studies)	75 (2%) ^^ (3 studies)	= 0.068

N=number of patients underwent this procedure. % per column total. ^^ total % < 100% as outcomes was not mentioned in all studies

I (inconsistency) was 68.8%; with significant Q test for heterogeneity ($p=0.04$); so random-effects model was chosen to assess safety; with overall RR= 1.33 and a 95% CI for (LRR) ranged from 0.707 to 2.510, with non-significant difference in safety in the CRT group compared to surgery group ($p > 0.05$) as shown in Table 12 & Figure 5.

We found 3 studies reported DMR rate simultaneously, with total number of patients (N=367).

Statistical-analysis as shown in Table 13; showed that fixed and random-effects models showed non-significant difference in DMR between the 2 groups ($p > 0.05$ respectively).

Table 12 statistical-analysis of (LRR) on CRT vs surgery usage - Risk Ratio

N	Study	CRT	Surgery	RR	95% CI	Z	P value	Weight (%)	
								Fixed	Random
1	Chen 2018	65/124	38/133	1.83	1.337 to 2.518			73.82	44.87
2	Kim2017	14/39	10/21	0.75	0.408 to 1.393			19.64	34.27
3	Masuda 2017	8/27	4/23	1.70	0.588 to 4.935			6.55	20.86
	T (fixed effects)	87/190	52/177	1.56	1.194 to 2.048	3.25	0.001**	100	100
	T (random effects)	87/190	52/177	1.33	0.707 to 2.510	0.886	0.376	100	100

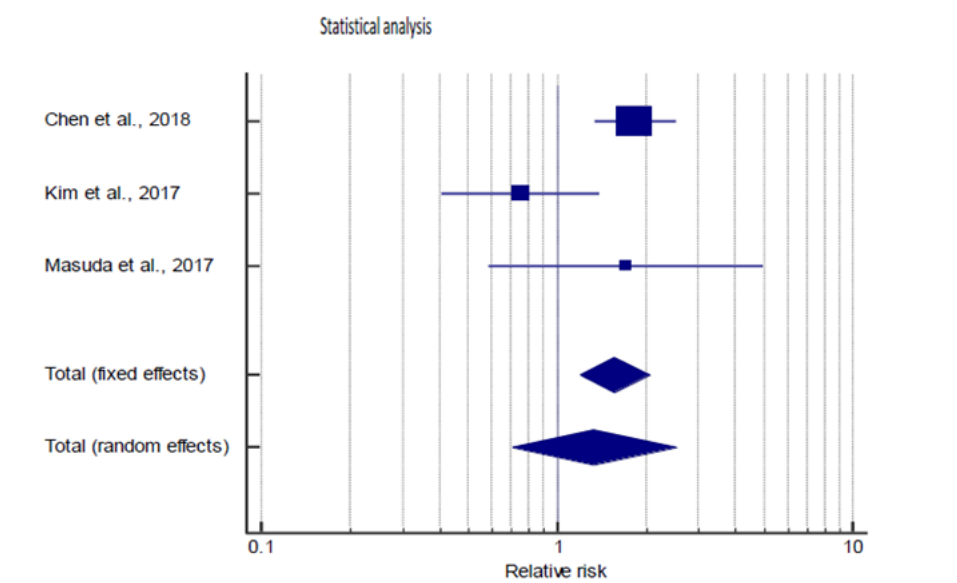


Figure 5 Forest plot of (LRR) on CRT vs. surgery usage - Risk Ratio.

I (inconsistency) was 79.3%; with highly significant Q test for heterogeneity ($p= 0.0079$); so random-effects model was chosen to assess safety; with overall RR= 0.9 and a 95% CI for (DMR) ranged from 0.453 to 1.788, with non-significant difference in safety in the CRT group compared to surgery group ($p > 0.05$) (Figure 6).

Two studies reported overall recurrence rate simultaneously, with total number of patients (N=307).

Statistical-analysis as shown in Table 14; fixed and random-effects model showed highly significant decrease in overall recurrence rate in favor of surgery studies ($p=0.001$ respectively).

I(inconsistency) was 0%; with non-significant Q test for heterogeneity ($p>0.05$); so fixed-effects model was chosen to assess safety; with overall RR=1.63 and a 95% CI for (overall recurrence rate) ranged from 1.225 to 2.177, with highly significant decrease in overall recurrence and increase in safety in favor of surgery studies ($p =0.001$) (Figure 7).

Two studies reported mortality rate simultaneously, with total number of patients (N=307).

Statistical-analysis as shown in Table 15; fixed and random-effects models showed non-significant difference in mortality rate between the 2 groups ($p>0.05$ respectively).

Table 13 Statistical-analysis of (Distant metastatic rate) on CRT vs surgery usage - Risk Ratio

N	Study	CRT	Surger y	RR	95% CI	Z	P value	Weight (%)	
								Fixed	Random
1	Chen 2018	31/124	28/133	1.18	0.758 to 1.860			38.49	37.36
2	Kim 2017	18/39	18/21	0.53	0.368 to 0.788			53.27	39.09
3	Masuda 2017	8/27	5/23	1.36	0.517 to 3.592			8.25	23.56
	T (fixed effects)	57/190	51/177	0.93	0.693 to 1.254	-0.463	0.643	100	100
	T (random effects)	57/190	51/177	0.90	0.453 to 1.788	-0.300	0.765	100	100

Table 14 Statistical-analysis of (overall recurrence rate) on CRT vs. surgery usage - Risk Ratio

N	Study	CRT	Surger y	RR	95% CI	Z	P value	Weight (%)	
								Fixed	Random
1	Chen 2018	65/124	44/133	1.58	1.181 to 2.126			94.3	94.37
2	Masuda 2017	8/27	3/23	2.27	0.681 to 7.578			5.63	5.63
	T (fixed effects)	73/151	47/156	1.63	1.225 to 2.177	3.345	0.001**	100	100
	T (random effects)	73/151	47/156	1.61	1.215 to 2.152	3.296	0.001**	100	100

Q test for heterogeneity = 0.32, degree of freedom (DF) = 1, p = 0.566, I^2 (inconsistency) = 0% and risk ratio (RR) = 1.63

Table 15 Statistical-analysis of (mortality rate) on CRT vs. surgery usage - Risk Ratio

N	Study	CRT	Surgery	RR	95% CI	Z	P value	Weight (%)	
								Fixed	Random
1	Chen 2018	62/124	60/133	1.10	0.857 to 1.433			90.45	56.70
2	Masuda 2017	6/27	13/23	0.39	0.178 to 0.868			9.55	43.30
	T (fixed effects)	68/151	73/156	0.96	0.760 to 1.234	-0.257	0.797	100	100
	T (random effects)	68/151	73/156	0.70	0.257 to 1.949	-0.669	0.503	100	100

Q test for heterogeneity = 6.03, degree of freedom (DF) = 1, p = 0.014*, I^2 (inconsistency)=83.4% and risk ratio (RR) = 0.7

I(inconsistency) was 83.4%; with significant Q test for heterogeneity (p=0.014); so random-effects model was chosen to assess safety; with overall RR=0.7 and a 95% CI for (mortality rate) ranged from 0.257 to 1.949, with non-significant difference in safety in the CRT group compared to surgery group (p>0.05) (Figure 8).

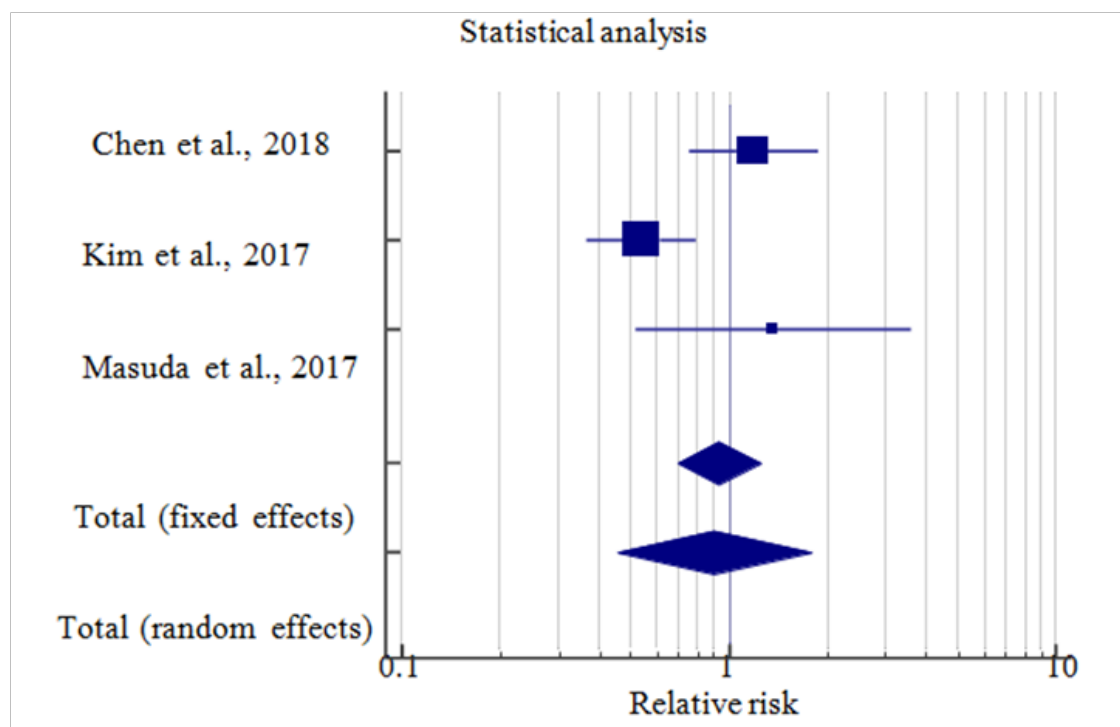


Figure 6 Forest plot of (DMR) on CRT vs. surgery usage - Risk Ratio.

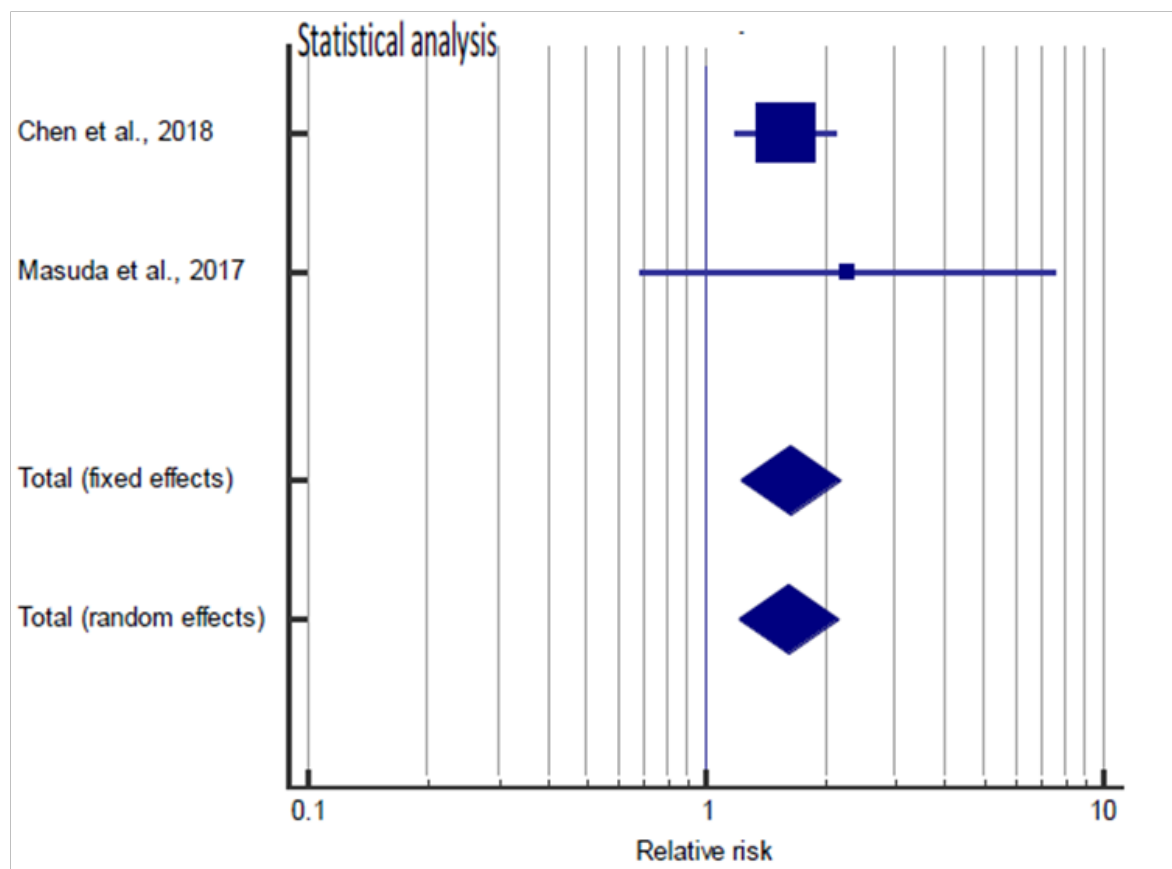


Figure 7 Forest plot of (overall recurrence rate) on CRT vs. surgery usage - Risk Ratio.

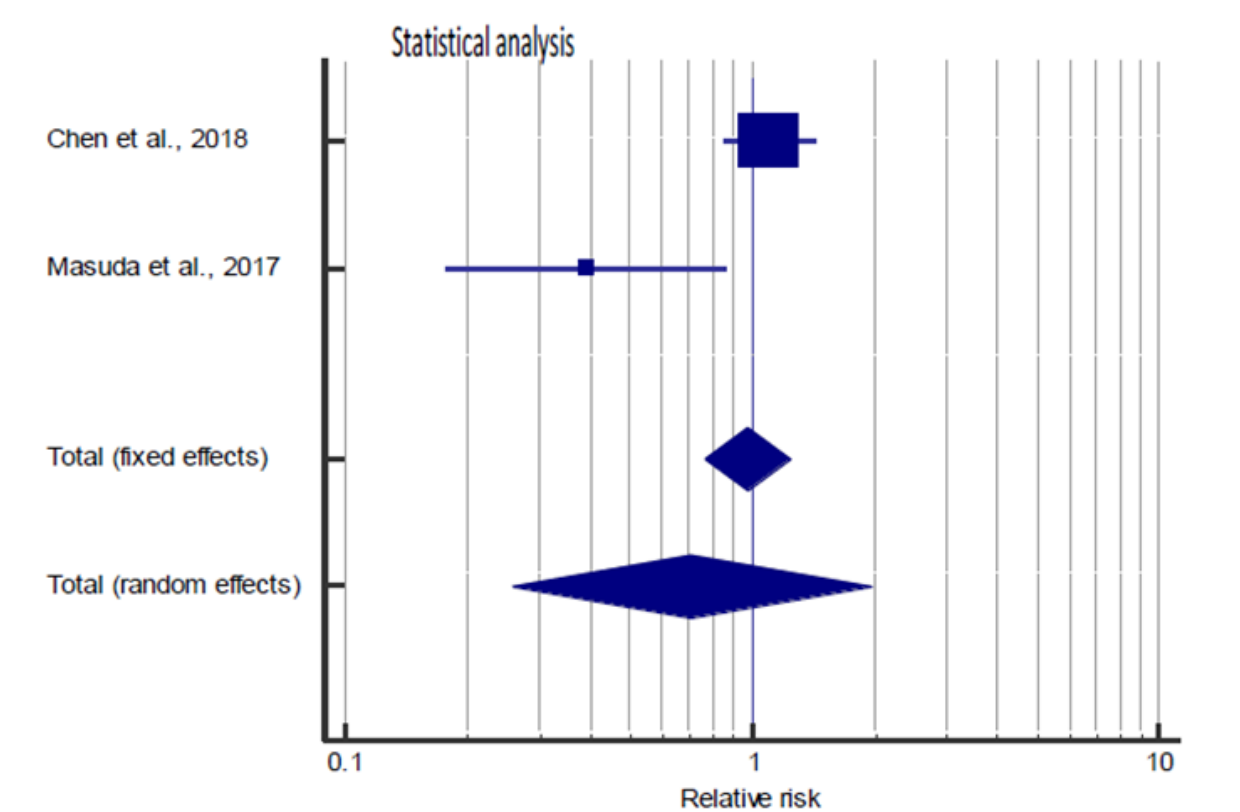


Figure 8 Forest plot of (mortality rate) on CRT vs. surgery usage - Risk Ratio.

Discussion

Hypopharyngeal cancer is a rare disease representing about 0.5% of all human malignancies with an incidence of less than 1 per 100 000 populations and constituting only 3-5% of all head and neck cancers. Hypopharyngeal cancers are often at an advanced stage at diagnosis and are associated with a poor prognosis.³ Therefore, the improvement of clinical outcomes for patients with hypopharyngeal SCC has been particularly challenging for head and neck surgeons and oncologists. Chemo-radiotherapy has been used for patients with advanced hypopharyngeal cancer with the aim of preserving the larynx. The reasons for the un-favorable prognosis of hypopharyngeal cancers are the strong tendency for extensive sub-mucosal spread, the early occurrence of regional lymphatic involvement, and the relatively high rate of distant spread.⁴ In the 1970s and 1980s, surgical resection followed by radiotherapy has been the standard treatment for advanced hypopharyngeal squamous cell carcinoma (HSCC).⁵ This radical approach of treatment, leads to the loss of natural speech function and impairment of swallowing ability with a consequent negative impact on the quality of life, and low cure rates, with reported 5-year survival between 20.0% and 50.0%.⁶ However, since the early 1990s, chemo-radiation (CRT) has become a valuable alternative treatment option. Due to organ preservation, it has been suggested that CRT is followed by a better long-term quality of life than after total laryngopharyngectomy (TLE), with similar survival.⁷

The Aim of our study is to collect the recent data about the different

modalities of management of advanced stage hypopharyngeal carcinoma (stage III and IV), and systematically review the outcomes of each modality and compare the efficacy of them. We found 21 studies that fulfilled all inclusion criteria. The included studies published between 2001-2018. Regarding the type of therapeutic interventions; 2 studies used surgery technique only; 13 studies used CRT technique only, while 6 studies compared both techniques. To the best of our knowledge, this is the largest systematic review in this subject. The total number of patients in all the included studies was 10539 patients; while the biggest study was by Shah et al.,¹ who studied 9106 patients; and the smallest study was by Suzuki G et al.,² who studied only 19 patients. We divided the included studies into

- A. Surgery treatment group (Surgery).
- B. CRT treatment group (CRT).

With comparing of the different outcomes:

The total number of patients in surgery group was 3584 patients (34%) in 8 studies, While CRT group; it was 6955patients (66%) in 19 studies.

Age, sex, and tumor stage have all been established as prognostic factors affecting survival in patients with HP SCC.

Overall survival, regarding surgery group was reported in 8 studies with total 1657patients achieved overall survival (46.23%); While in CRT group, it was reported in 18 studies with total 2995patients

achieved overall survival (43%). Comparative study between the 2 groups revealed decrease in overall survival rate; in CRT group; compared to surgery group; with significant statistical difference ($p=0.019$). According to Taha and his colleagues in 2013 there was no survival difference between the organ preservation intended therapy and radical surgery groups. Patients who received concurrent radio-chemotherapy had a better chance of survival with a preserved larynx compared with patients who underwent surgery.⁸ It is a well-known fact that postoperative RT or CRT improves tumor control in head and neck cancer patients with high-risk features. However, the cost of using adjuvant RT or CRT to improve disease control and survival may be substantial, namely increased treatment-related toxicities and prolongation of the total treatment time. In unsuccessful organ preservation attempts, failures in function preservation may result from either toxicity from aggressive CRT, extensive tumor infiltration into the organ at the time of diagnosis, or from progression of disease.⁷ In the present study Success rate was reported in 7 studies with total 192 patients achieved full control by surgical management (5.35%). While as reported in 15 studies with total 436 patients achieved full response on CRT (6.26%). Comparative study between the 2 groups revealed non-significant difference as regards success rate ($p>0.05$).

A study by Brasilino de Carvalho in 1998⁹ has analyzed data of 170 patients with laryngeal and hypopharyngeal cancer and reported that 5-year disease free survival of patients without cervical metastases is significantly higher than that in patients with cervical metastases (56.8% vs. 10.2%, $p<0.0001$).

Patients who achieved favorable outcomes were pooled to evaluate efficacy and risk ratio via:

- a. Achievement of overall survival rate.
- b. Achievement of success rate.

Six studies reported overall survival rate simultaneously, with total number of patients ($N=9709$).

Statistical-analysis study showed that; fixed-effects model showed significant increase in overall survival rate in favor of surgery studies, while random-effects model showed non-significant difference between the 2 groups ($p=0.013$, $p>0.05$ respectively). I² (inconsistency) was 82%; with highly significant Q test for heterogeneity ($p<0.01$). So random-effects model was chosen to assess efficacy; with overall $RR=0.9$ and a 95% CI for achievement of (overall survival) ranged from 0.662 to 1.231, with non-significant difference in efficacy in the CRT group compared to surgery group ($p>0.05$). Kim and others considered that nonsurgical therapy (induction chemotherapy plus RT) is an effective strategy to achieve organ preservation without compromising the survival of locally advanced hypopharyngeal carcinoma patients.⁶ Five studies reported success rate simultaneously, with total number of patients ($N=603$). Statistical-analysis study showed that; fixed-effects model showed significant increase in success rate in favor of CRT studies, while random-effects model showed non-significant difference between the 2 groups ($p=0.01$, $p>0.05$ respectively). I² (inconsistency) was 85.5%; with highly significant Q test for heterogeneity ($p<0.01$); so random-effects model was chosen to assess efficacy; with overall $RR=1.02$ and a 95% CI for achievement of (success rate) ranged from 0.664 to 1.584, with non-significant difference in efficacy in the CRT group compared to surgery group ($p>0.05$).

A matched-pair analysis by Rades and his colleagues in 2011, compared definitive radio-chemotherapy to surgery followed by radio (chemo) therapy as treatment strategies for T3/4 larynx and hypopharynx cancer. Overall survival rates were 67% and 63%, respectively ($p=0.95$) these did not result in significantly worse overall survival.¹⁰ The better results in this study may be due to the hidden selection biases that could not be excluded due to the retrospective nature of the study. Overall recurrence rate reported in 2 studies presenting surgical management outcomes with total 47 patients had overall recurrence (1.3%). in 9 studies presenting CRT total 198 patients had overall recurrence rate (2.84%). Comparative study between the 2 groups revealed; highly significant increase in overall recurrence rate in CRT group compared to surgery group with highly significant statistical difference ($p<0.01$). According to Vaidya and his colleagues in 2001 patients who underwent surgical resection 18 out of 24 patients showed recurrences for those who had cervical metastases with extra-capsular nodal spread involving distant sites, especially to the lung.¹¹ Local recurrence rate was reported in 4 studies regarding surgery group with total 80 patients had Local recurrence rate (2.23%), otherwise CRT group, LRR was reported in 6 studies with total 125 patients had local recurrence rate (1.79%). Distant metastatic rate was reported in 4 studies discussing surgical management of advanced hypopharyngeal carcinoma with total 59 patients had distant metastatic rate (1.64%). in 12 studies dealing with CRT total 137 patients had distant metastatic rate (1.96%).

Mortality rate of surgery was reported in 3 studies with 75 patients with disease specific mortality (2%), but 8 studies presenting CRT with 186 patients died from the disease (2.67%). Comparative study between the 2 groups revealed non-significant difference as regard local recurrence rate, distant metastatic rate, and mortality rates ($p>0.05$). A significant indicator of recurrence was margin status. It is known that inadequate resection can lead to increased likelihood of disease recurrence and poorer odds of survival for patients.¹² Ravasz and his colleagues in 1991 has shown that loco-regional recurrence observed in 20% of 80 head and neck cancer patients is correlated with tumor positive margins.¹³ For Rades and his colleagues radio-chemotherapy did not result in significantly worse outcomes in terms of loco-regional management and metastasis-free survival. Two-year loco-regional control rates were 75% for surgery plus radio-chemotherapy and 66% for radio-chemotherapy ($p=0.39$). Metastases-free survival rates were 76% and 77%, respectively ($p=0.76$).¹⁰ The rarity of this disease, and the time required for data collection explains in part the absence of a randomized trial undertaken to evaluate the role-played by CRT in the treatment of advanced hypopharyngeal cancer. Additionally, patients longing for preserving their larynx probably will not be willing to participate in a randomized clinical trial offering a 50% chance of larynx preservation, as a non-surgical option is available.¹⁴

In favor of CRT as reported in 10 studies 311 patients achieved larynx preservation (4.47%), failure rate was reported in 5 studies with 97 patients whose treatment failed (1.39%).

While mean 9 studies reported complications rate with 144 patients (2%) had complications. None of larynx preservation, failure rate or complications rate were reported regarding surgery group. Considering that larynx preservation is such an important issue, despite the absence of prospective data, definitive radio-chemotherapy does not seem to be inferior to surgery plus radiotherapy for locally advanced hypopharynx cancer, and allows for a significant higher larynx preservation rate.¹⁴

Also, Study by Rades and his colleagues: radio-chemotherapy resulted in a considerably higher rate of larynx preservation as compared with the primary surgical approach.¹⁰ Patients who reached serious adverse events were pooled to assess safety by assessing:

- a. Overall recurrence rate.
- b. Local recurrence rate.
- c. Distant metastatic rate.
- d. Mortality rate.

Three studies reported LRR simultaneously, with total number of patients (N=367). Statistical-analysis study showed that; fixed-effects model showed significant decrease in local recurrence rate in favor of surgery studies, while random-effects model showed non-significant difference between the 2 groups ($p=0.001$, $p>0.05$ respectively).

I² (inconsistency) was 68.8%; with significant Q test for heterogeneity ($p = 0.04$). So random-effects model was chosen to assess safety; with overall recurrence rate = 1.33 and a 95% CI for (Local recurrence rate) ranged from 0.707 to 2.510, with non-significant difference in safety in the CRT group compared to surgery group ($p > 0.05$).

Three studies reported distant metastatic rate simultaneously, with total number of patients (N=367).

Statistical-analysis study showed that; fixed and random-effects models showed non-significant difference in distant metastatic rate between the 2 groups ($p>0.05$ respectively).

I² (inconsistency) was 79.3% with highly significant Q test for heterogeneity ($p = 0.0079$); so random-effects model was chosen to assess safety; with overall recurrence rate = 0.9 and a 95% CI for (Distant metastatic rate) ranged from 0.453 to 1.788, with non-significant difference in safety in the CRT group compared to surgery group ($p > 0.05$).

Two studies reported overall recurrence rate simultaneously, with total number of patients (N=307).

Statistical-analysis study showed that; fixed and random-effects models showed highly significant decrease in overall recurrence rate in favor of surgery studies ($p=0.001$ respectively). I² (inconsistency) was 0% with non-significant Q test for heterogeneity ($p>0.05$); so fixed-effects model was chosen to assess safety; with overall recurrence rate=1.63 and 95% CI for (overall recurrence rate) ranged from 1.225 to 2.177, with highly significant decrease in overall recurrence and increase in safety in favor of surgery studies ($p=0.001$). Two studies reported mortality rate simultaneously, with total number of patients (N=307). Statistical-analysis study showed that; fixed and random-effects models showed non-significant difference in mortality rate between the 2 groups ($p>0.05$ respectively). I² (inconsistency) was 83.4%; with significant Q test for heterogeneity ($p=0.014$); so random-effects model was chosen to assess safety; with overall recurrence rate= 0.7 and a 95% CI for (mortality rate) ranged from 0.257 to 1.949, with non-significant difference in safety in the CRT group compared to surgery group ($p > 0.05$). Urba and colleagues reported 79% of patients with grade 3 and 4 toxicity treated with CRT for carcinoma in the hypopharynx or base of the tongue.¹⁵ Moreover, the functional sparing of the laryngo-pharynx is not always granted with such protocols. Treatment related toxicity; the need for

permanent gastrostomy tube placement and overall preservation of laryngo-esophageal function remains low.¹⁶ In the advanced stage setting, CRT is frequently proposed for patients in whom functional status has not been irreversibly compromised. Otherwise, a primary surgical approach followed by postoperative RT is typically adopted. The shift to organ preservation protocols worldwide, are mainly due to improved laryngo-pharyngeal preservation in such cases. However, one should not miss that these protocols have high toxicity rate and need intensive patient care and monitoring by experienced multi-disciplinary teamwork.⁴

Conclusions

Hypopharyngeal cancer is a distinct clinical entity of head and neck cancer with a relatively poor prognosis. In summary, the survival outcomes for locally advanced hypopharynx cancer in the present study are consistent with other studies in the literature. The treatment approach had a significant impact on OS and RR, as described in other series. Given the equivalence between these two strategies suggested in several series, definitive CRT seems to be an advantageous option as it improves organ preservation and, consequently, the functional outcome. Recent developments in chemo-radiation treatment techniques could hopefully increase tumor management and survival rates.

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Conflict of interests

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