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TREATMENT OF CERVICAL ESOPHAGEAL CARCINOMA: SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Objectives. Up to date managing a cervical esophageal carcinoma (CEC) has remained a controversial challenge. The choice of treatment is still uncertain. In the present review we attempted to assess eligibility of surgery in treatment of CEC. **Material and Methods.** We have enquired particular publication databases and the enquiries yielded 24 contributions matching study selection criteria such as (1) original articles published from 2000 to 2022, (2) primary tumor localization in the cervical esophagus, (3) squamous cell carcinoma, (4) available characteristics of studied groups (age, sex, T, N, M, stage), (5) detailed description of curative procedures (radiation therapy, chemotherapy, surgery), (6) information about overall survival. These publications represented two arms of 14 surgical and 17 non-surgical subgroups to analyze. Individual patient data and parameter estimates have been renewed on the basis of original Kaplan–Meier curves plotted. **Results.** The analysis revealed a highly heterogeneous (I^2=83.76 %; 95 % CI, 71.40–92.16) random effects model. Including a surgical option into treatment of CEC did not affect 3-year overall survival (p=0.665); 46.4 % (95 % CI, 37.4–55.6) *vs* 43.7 % (95 % CI, 35.3–51.6), respectively. Possibilities of surgical and non-surgical modalities employment were discussed. **Conclusion.** In treatment of CEC CRT and surgery are non-inferior to each other. These modalities are evenly associated with posterior side effects and complications, which adversely affect functional outcomes and survival. The choice of a treatment mode may depend on tumor response to induction therapy. The latter demands further investigations.

Key words: cervical esophageal carcinoma, chemoradiation therapy, surgery.

ЛЕЧЕНИЕ РАКА ШЕЙНОГО ОТДЕЛА ПИЩЕВОДА: СИСТЕМАТИЧЕСКИЙ ОБЗОР И МЕТААНАЛИЗ

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Аннотация

Лечение рака шейного отдела пищевода (РШП) до настоящего времени является предметом дискуссии. Выбор метода лечения все еще остается неопределенным. **Цель исследования** – оценить целесообразность хирургического вмешательства при лечении РШП. **Материал и методы.** Произведен поиск оригинальных исследований в базах данных. В настоящий обзор включено 24 статьи, соответствующие критериям включения для анализа, таким как (1) оригинальные исследования, опубликованные с 2000 по 2022 г., (2) первичная локализация опухоли в шейном отделе пищевода, (3) плоскоклеточный рак, (4) наличие клинической характеристики исследуемых групп (возраст, пол, T, N, M, клиническая стадия),

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(5) подробное описание применяемых методов лечения (лучевая терапия, химиотерапия, хирургические операции), (6) наличие информации об общей выживаемости. Эти публикации включали две группы из 14 хирургических и 17 нехирургических подгрупп. Персональные данные пациентов и оценка параметров были восстановлены на основании первичных графиков кривых Каплана–Мейера. **Результаты.** Анализ выявил выраженную гетерогенность (I^2=83,76 %; 95 % ДИ, 71,40–92,16) «random effects» модели. Использование хирургического метода в лечении РШП не повлияло на 3-летнюю общую выживаемость (p=0.665); 46.4 % (95 % ДИ 37,4–55,6) против 43,7 % (95 % ДИ 35,3–51,6) соответственно. Были обсуждены возможности применения хирургических и нехирургических методов лечения. **Заключение.** В лечении РШП химиолучевая терапия и радикальные операции взаимно неинфериорны. Эти методы лечения в равной степени сопряжены с развитием нежелательных эффектов и осложнений, что может ухудшать функциональный результат и показатели выживаемости. Выбор метода лечения может зависеть от степени ответа на индукционную терапию. Последний аспект требует дальнейшего изучения.

Ключевые слова: рак шейного отдела пищевода, химиолучевая терапия, хирургия.

Introduction

Up to date managing a cervical esophageal carcinoma (CEC) has remained a controversial challenge. Firstly, the choice of treatment is still uncertain. Low incidence of esophageal carcinoma (5.33 per 100,000 in the Russian Federation) [1] and infrequent damaging of its cervical part (approximately 5 % of all cases) [2] prevent from recruiting plentiful groups of patients and pursuing well-designed prospective trials. The latter are usually rare and retrospective [2–4].

As technologies of radiation therapy and chemotherapy have been improved, concurrent chemoradiation (CRT) represents the current tendency in treatment of CEC, which was assumed in some worldwide clinical guidelines [5, 6]. Due to the tumor localization and technical complexity, surgery is not strongly discommended to be a principal curative option. Nevertheless, it is employed in some clinics and is of interest currently [7].

In the present review we attempted to assess eligibility of surgery in treatment of CEC.

Material and Methods

The search strategy was conducted using the MEDLINE (www.pubmed.com), EMBASE (www.embase.com), Cochrane Central Register of Controlled Trials (www.cochranelibrary.com) databases with the following search terms: (proximal esophageal cancer) OR (upper esophageal cancer) OR (carcinoma of the cervical esophagus). Total 643 sources were found. Reviews, monographs, textbooks, case reports, and non-English-written or non-full-text publications were rejected. Study selection criteria were (1) original articles published from 2000 to 2022, (2) primary tumor localization in the cervical esophagus with possible tumor extension to a hypopharinx or into thoracic inlet, (3) squamous cell carcinoma, (4) available characteristics of studied groups (age, sex, T, N, M, stage), (5) detailed description of curative procedures (radiation therapy, chemotherapy, surgery), (6) information about overall survival. Finally, on the basis of these criteria 24 original contributions were extracted for analysis by two investigators. As a rule, information about group characteristics or overall survival was incomplete, which required its recalculation or data restoration.

Comparison of surgical and non-surgical groups was presented in only several publications, that is why we could not estimate an «effect size» (ES) as a classical «hazard ratio». Thereafter, in the framework of meta-analysis main parameter estimates were a median of overall survival and its confidence interval (CI) (median, 95 % CI), and 1-, 3-, 5-year overall survival (OS) with its standard error (SE) (OS ± SE). Accessible and determined subgroups of patients presented in original articles were analyzed. In 24 selected publications we identified 31 studied subgroups with known characteristics and OS. Unfortunately, in the absolute majority of studies information about OS was reduced or incomplete (without announced SE or/and CI). Thereby we were encouraged to restore individual patient data (IPD) on the basis of Kaplan-Meier curves plotted in all articles for all 31 subgroups.

At the first stage original Kaplan-Meier curves saved as PDF files were redrawn and processed precisely using Adobe Photoshop CS6 v 13.1.2x64. These images were digitized using OriginPro 2022 v.9.9.0.225 (SR1). Then for the purpose of IPD restoration renewed Kaplan-Meier graph coordinates were exported into special IPDfromKM software written in programming language R [8]. The target parameters (medians, CI, OS, SE) were estimated employing the same software. Then all subgroup characteristics and restored survival parameter estimates were put into an intermediate Excel file, formatted, and exported into a statistical program package. Accuracy of IPD reconstruction was checked by intrinsic IPDfromKM tests including the Kolmogorov-Smirnov one. With a probability more than p=0.97 all restored data coincided with their original counterparts. Differences between reported original and estimated values did not exceed tenths. Characteristics of 31 subgroups from 24 selected publications are shown in Table 1.

Not all studies were dedicated to limited cervical localization of the tumor. Many authors included cancer extension either in a hypopharinx or in an upper thoracic esophagus or both. All subgroups were divided into surgical and non-surgical arms. According to original information, particular types of treatment and their proportions in the subgroups were registered. Sex composition was recalculated as a females/males

Table 1/Таблица 1

Characteristics of 31 studied subgroups from 24 original publications

Характеристики 31 группы исследования из 24 оригинальных публикаций

Parameter (data format)/Показатель (формат данных)	Values/Значения
Tumor Localization (PEJ/C/M)/ Локализация опухоли (ШФ/Ш/См)	1/14/16
Mode of Treatment (CRT/SurgCRT/SurgRT/SurgCT)/ Вариант лечения (ХЛТ/ХирХЛТ/ХирЛТ/ХирХТ)	17/9/4/1
Subgroup (surgical/non-surgical)/Группа (хирургическая/нехирургическая)	14/17
Proportion of RT in any treatment mode given/ Доля ЛТ при любом варианте лечения (Q25-med-Q75)	0.00 – 0.00 – 0.15
Proportion of CRT in any treatment mode given/ Доля ХЛТ при любом варианте лечения (Q25-med-Q75)	0.14 – 0.87 – 1.0
Number of patients in subgroups (total, min, max, median)/ Количество пациентов в группах (всего, мин., макс., медиана)	1996, 11, 209, 56
Average Age/Средний возраст (min – max; mean ± SD)	54 – 68; 61.20 ± 3.41
Sex (females/males)/ Пол (женщины/мужчины) (min – max; mean ± SD)	0.00 – 0.91; 0.33 ± 0.22
Average Stage in a Subgroup/ Средняя клиническая стадия в группе (min – max; mean ± SD)	1.68 – 3.74; 2.66 ± 0.42

Note: PEJ – pharyngo-esophageal junction; C – pure cervical; M – mixed; CRT – chemoradiation therapy; SurgCRT – combination of surgery and CRT; SurgRT – combination of surgery and radiation therapy; SurgCT – combination of surgery and chemotherapy. Subsequence of CRT and surgery (prior or posterior) was not of regard.

Примечание: ШФ – шейная локализация с переходом на гипофаринкс; Ш – только шейная; См – смешанная; ХЛТ – химиолучевая терапия; ХирХЛТ – сочетание хирургического лечения с ХЛТ; ХирЛТ – сочетание хирургического лечения с лучевой терапией; ХирХТ – сочетание хирургического лечения с химиотерапией. Последовательность ХЛТ и хирургического лечения (до или после) не учитывалась.

ratio per subgroup. Categories T, N, M were not represented carefully in all studies; hence, we delivered a calculated average clinical stage per subgroup as this information was accessible.

Descriptive statistics, contingency tables, methods of classical and Bayesian meta-analysis were implemented in JASP (Version 0.16.4) statistical software used.

Results

In total, 31 subgroups comprised 1,996 patients. In 5 studies the survival median was not achieved, that is why the average median was estimated among 26 of 31 subgroups of patients (Table 2). For this purpose Bayesian meta-analysis was employed as its computations maintain restored CIs for medians, whereas median SEs were not recalculated using original data. A treatment effect size itself did not matter because all medians were evidently expected to be higher than zero. In view of subgroup and treatment diversity, a «random effects» statistical model was considered to be the only possible a priori. Calculated posterior probability of the «random effects» model with non-zero ES was $p(H1_{random})=1.0$. Average OS medians for different models and between-group variance are presented in Table 3.

One-year OS estimates are shown in Figure 1. The model was highly heterogeneous (I^2=89.63 %; 95 % CI, 82.71–94.44). The average 1-year OS was 76.2 % (95 % CI, 71.3–81.1). Predictors of OS were of undoubted interest. (1) The proportion of patients who received radiation therapy (RT), (2) the proportion of patients who received CRT, (3) the average age, (4) the females/males ratio, (5) the average stage of tumors were regarded as potential covariates (interval variables). (1) The mode of treatment (CRT, surgery + + CRT, surgery + RT, surgery + chemotherapy), (2) the type of treatment (including surgery, excluding surgery), (3) tumor localization (pharyngo-esophageal junction, cervical, mixed) were included as factors (nominal variables). Results of meta-regression are presented in Table 4. Only the average stage and tumor localization with extension to hypopharynx affected 1-year survival significantly.

Estimates of 3-year OS are shown in Figure 2. This model was heterogeneous too (I^2=83.76 %; 95 % CI, 71.40–92.16). Mean 3-year OS was 45.2 % (95 % CI, 39.4–51.0). None of potential predictors mentioned above (p>0.08) including the average tumor stage (p=0.067) influenced 3-year OS. Five-year OS was estimated among 27 of 31 subgroups only because there was no information about it in 4 publications (Figure 3). Mean 5-year OS was 36.7 % (95 % CI, 31.3–42.4). Analogously the model was highly heterogeneous (I^2=79.97 %; 95 % CI, 62.49–91.60) and predictors of OS were not included (p>0.09) either.

All 31 Kaplan-Meier curves of OS were fitted by complements of several theoretical cumulative distribution functions. In 15 publications the log-logistic function exhibited the best approximation, in 14 ones the log-normal fitting was excellent, and only in 2 subgroups the Weibull fitting function was predominant. Subsequent calculation of respective hazard risk functions demonstrated either the initially high and

Table 2/Таблица 2

Medians of Overall Survival per Subgroup

Медианы общей выживаемости в группах

Author (arm)/ Автор (вид лечения)	Observed/ Наблюдаемые	Estimated/Рассчитанные		
		Mean/ Среднее[a]	Lower/ Нижняя[a]	Upper/ Верхняя[a]
Du X.X. et al., (2019) (CRT)	44.960	37.443	25.146	50.783
Li C.C. et al., (2021) (CRT)	21.330	22.211	13.203	30.960
Sakanaka K. et al., (2018) (CRT)	60.110	31.191	12.411	52.689
Li X. et al., (2021) (PEJ, CRT)	38.800	31.105	15.374	48.179
Li H.X. et al., (2018) (CRT)	36.000	33.398	23.860	43.354
Chen P. et al., (2020) (Surgery + CRT)	59.452	45.550	31.270	60.717
Chen N.B. et al., (2020) (3D-CRT)	35.860	27.417	8.674	46.654
Chen N.B. et al., (2020) (IMRT CRT)	43.270	28.352	10.111	47.467
Valmasoni M. et al., (2018) (CR, Surgery + CRT)	20.870	23.495	8.301	38.283
Valmasoni M. et al., (2018) (CR, CRT)	45.850	37.805	24.742	51.227
Valmasoni M. et al., (2018) (PR, SD, PD, Surgery + CRT)	20.310	21.177	13.907	28.257
Valmasoni M. et al., (2018) (PR, SD, PD, CRT)	9.966	11.862	5.123	18.357
Cao C.N. et al., (2014) (Surgery + RT)	26.449	26.305	14.112	38.453
Huang S. et al., (2008) (CRT)	12.000	12.860	7.990	17.535
Gkika E. et al., (2014) (CRT)	17.970	18.740	12.510	24.846
Herrmann E. et al., (2017) (CRT)	40.640	27.770	8.350	48.500
Zhao L. et al., (2017) (CRT)	41.360	35.692	23.602	48.738
Daiko H. et al., (2007) (Surgery + RT)	21.730	23.223	11.696	35.048
Sun F. et al., (2014) (Gastric Transpos., Surgery + RT)	46.300	27.259	7.670	48.630
Triboulet J.P. et al., (2001) (Surgery + CRT)	16.780	17.298	12.855	21.864
Zhang P. et al., (2015) (CRT)	27.290	27.129	20.490	33.781
Tong D.K. et al., (2011) (Surgery + CRT)	19.580	20.719	12.497	28.966
Tong D.K. et al., (2011) (CRT)	24.940	25.087	15.736	34.395
Makino T. et al., (2016) (LNP, Surgery + CRT)	15.570	16.951	9.883	23.864
Wang W. et al., (2020) (Surgery + Chem)	31.830	28.764	14.739	43.354
Yamada K. et al., (2006) (CRT)	13.130	23.806	4.087	43.220

Note: [a] – posterior mean and 95 % credible interval estimates from the random effects model; CRT – chemoradiation therapy; PEJ – pharyngo-esophageal junction; CR, PR, SD, PD – complete response, partial response, stable disease, progressive disease respectively; LNP – larynx non-preserving.

Примечание: [a] – апостериорные средние и 95 % доверительный интервал рассчитаны исходя из random effects модели; CRT – химиолучевая терапия; PEJ – глоточно-пищеводное соединение; CR, PR, SD, PD – полный ответ, частичный ответ, стабилизация опухоли, прогрессирование опухоли соответственно; LNP – без сохранения гортани.

Table 3/Таблица 3

Posterior Estimates (Medians) per Model

Апостериорные оценки медиан для различных моделей

Model/Модель		Mean/Среднее	SD	95 % Confidence Interval/ Доверительный интервал		BF_{10}
				Lower/Нижняя	Upper/Верхняя	
Fixed effects	μ	20.250	0.985	18.326	22.160	$1.115\times10^{+89}$
Random effects	μ	25.991	2.799	20.693	31.719	$1.870\times10^{+7}$
	τ	10.302	2.354	6.387	15.447	$6.410\times10^{+6}$
Averaged/Усредненная	μ	22.948	3.516	18.558	30.581	$1.870\times10^{+7}$
	τ					$6.410\times10^{+6}$

sharply decreased risk (Weibull fitting) or (in the majority of cases) an accelerated failure time model with the increasing risk within the initial surveillance period (Q25=6.33 mo, Q50=11.0 mo, Q75=16.2 mo) followed by the decreasing risk.

Discussion

We believe the present analysis supports uncertainty of the CEC treatment approach. Including the surgical option exhibits its non-inferiority in comparison with CRT alone. In none of non-surgical subgroups analyzed radiation therapy was employed

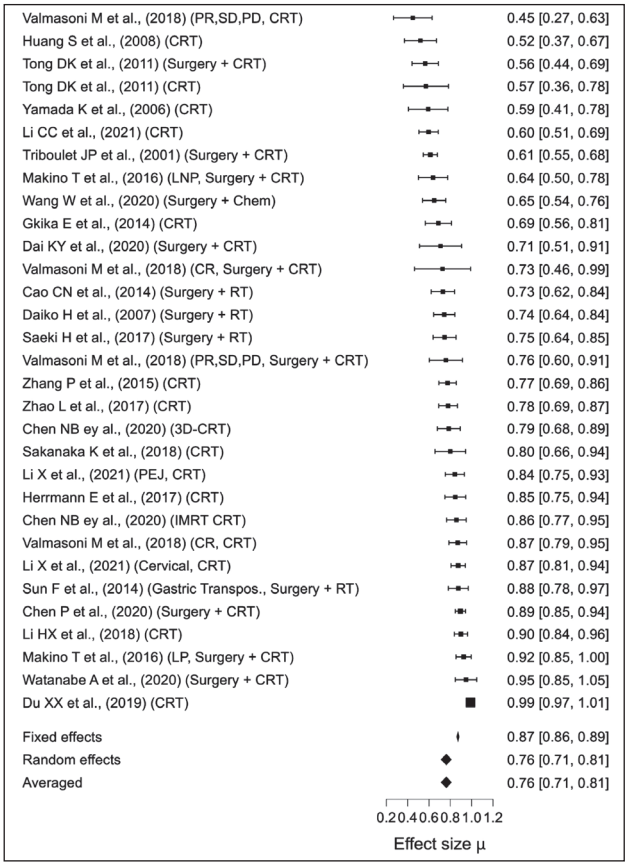

Fig. 1. Forest plot of 1-year overall survival.
(I^2=89.63 %; 95 % CI, 82.71–94.44)
Рис. 1. Forest plot 1-летней общей выживаемости.
(I^2=89,63 %; 95 % CI, 82,71–94,44)

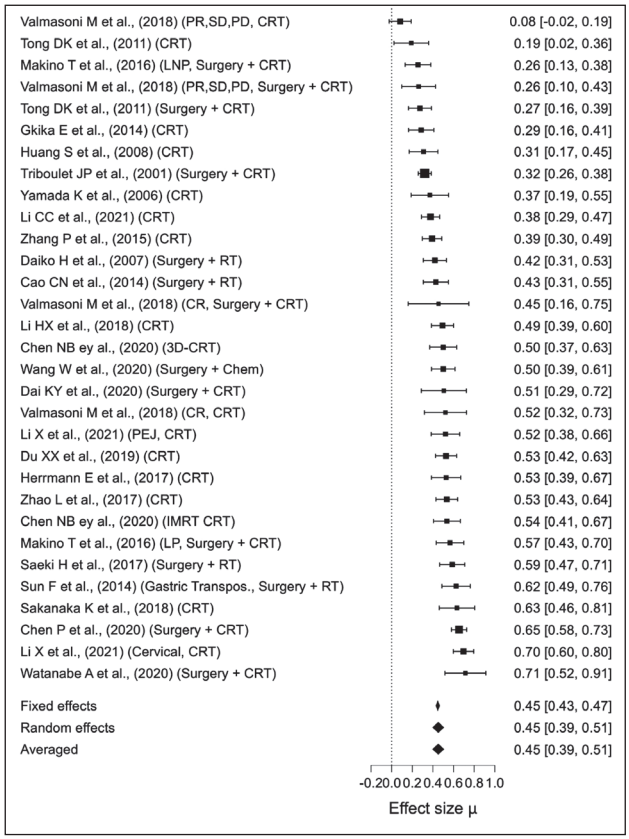

Fig. 2. Forest plot of 3-year overall survival.
(I^2=83.76 %; 95 % CI, 71.40–92.16)
Рис. 2. Forest plot 3-летней общей выживаемости.
(I^2=83,76 %; 95 % CI, 71,40–92,16)

as a single modality. Concurrent CRT for CEC using linear accelerators became a treatment of choice [3, 9–13]. On the other hand, all surgical patients received RT, or chemotherapy, or CRT predominantly as a preoperative procedure [9, 14–16]. Curative modalities assessed in the present meta-analysis comprising more than 1,900 patients were not revealed as significant predictors exerting influence on OS. The significant average stage is trivial and should not be discussed. Significant association of 1-year OS with a tumor site, which was demonstrated, coincides with the assumed statement that hypopharingeal and esophageal tumors represent different entities distinguished in their behavior, aggressiveness, and treatment approaches [17, 18]. Hence, an implicit tumor station in borderline esophageal areas may influence statistical inference.

Heterogeneity was anticipated to be high. A lot of factors affecting OS could not been regarded objectively because of a limited number of subgroups and different study designs as well. In original publications such points as diverse as preoperative or postoperative RT, total doses of irradiation, variable chemotherapeutical regimes and their combinations, and different tumors (resectable or non-resectable) are discussed. Certainly, all these factors could impact OS. As per low incidence of the carcinoma discussed such precise stratification

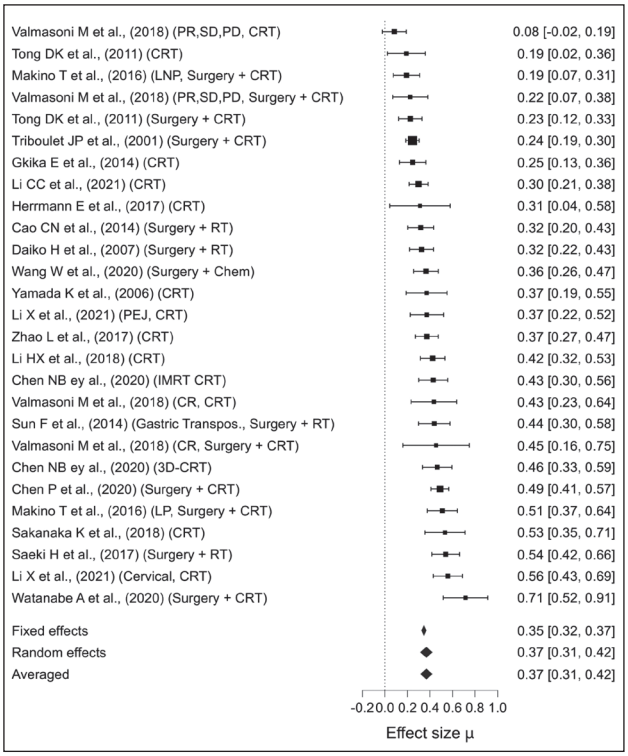

Fig. 3. Forest plot of 5-year overall survival.
(I^2=79.97 %; 95 % CI, 62.49–91.60)
Рис. 3. Forest plot 5-летней общей выживаемости.
(I^2=79,97 %; 95 % CI, 62,49–91,60)

Table 4/Таблица 4

Predictors of 1-year Overall Survival
Предикторы 1-летней общей выживаемости

Variables/Переменные	Coefficients/Коэффициенты			
	Estimate/Оценка	SE	z	p
Intercept/Интервал	1.410	0.547	2.579	0.010
Proportion of RT/Доля ЛТ	0.070	0.163	0.429	0.668
Proportion of CRT/Доля ХЛТ	0.205	0.148	1.384	0.166
Average Age/Средний возраст	-4.202×10^{-4}	0.008	-0.051	0.959
Female/Male Женщины/Мужчины	0.113	0.136	0.830	0.407
Average Stage/Средняя стадия	-0.294	0.105	-2.809	0.005
Treatment (Surgery + CRT)/Лечение (хирургия + ХЛТ)	0.008	0.084	0.090	0.929
Treatment (Surgery + Chemotherapy)/ Лечение (хирургия + химиотерапия)	-0.222	0.177	-1.255	0.210
Treatment (Surgery + RT)/Лечение (хирургия + ЛТ)	0.091	0.125	0.728	0.466
Localization (Mixed)/Локализация (смешанная)	-0.089	0.054	-1.644	0.100
Localization (PEJ)/Локализация (PEJ)	0.357	0.171	2.085	0.037

Note: Wald test; RT – radiation therapy; CRT – chemoradiation therapy; PEJ – pharyngo-esophageal junction.

Примечание: использовался Wald-тест; ЛТ – лучевая терапия; ХЛТ – химиолучевая терапия; PEJ – глоточно-пищеводное соединение.

was believed to be extremely restricted. Nevertheless, the main point of what role surgery plays in treatment of CEC is quite evident. Even in the framework of univariate analysis, including the surgical component (944 of 1,996 patients) did not result in alteration of 3-year OS (p=0.665); 46.4 % (95 % CI, 37.4–55.6) *vs* 43.7 % (95 % CI, 35.3–51.6).

The surgical option in treatment of CEC may be discussed in terms of its competitive advantage over CRT. Surgery provides R0 radical tumor excision. Pathologist's examination of the removed specimen improves tumor staging and assessment of pathomorphism. Lymph node dissection increases local and regional tumor control. However, surgery for CEC has its particularities. According to anatomical complexity and loco-regional extension the tumor frequently becomes non-resectable or requires resection of adjacent organs. R0-procedure achieved by extended laryngo-pharyngo-esophagectomies may have a disabling outcome [14, 17, 19]. Gastro-intestinal integrity restoration requires complex esophagoplasty or/and pharyngoplasty [2, 14, 17, 20], including visceral grafts transposition and autotransplantation [2, 14, 17, 19, 21]. R0 resection may fail [10, 17, 19] whilst R1 procedure should not be regarded as lacking oncology essence [10, 17]. Surgery for CEC may be accompanied by postoperative complications. Anastomotic leakage, transplant necrosis, pleural effusion, pneumonia, and chylothorax are the most life-threatening. Complications may appear in 29.1–44.7 %, mortality may reach 8.1 % [17, 19–21]. All these factors eventuate in some considerable sequels. Firstly, patients frequently reject disabling surgery. Secondly, because of their complexity such surgery cannot be feasibly reproduced and remains a prerogative of special high-volume centers. Thirdly, non-inferior OS and organ-preserving character make CRT a more rational modality. However, there are contributions which exhibit excellent immediate, functional, and long-term outcomes [2].

It should be noted that RT for CEC is commonly used in a concurrent regime as well as in combination with two-component chemotherapy, which increases aggressiveness of the mode and induces complications or adverse effects onset. Majority of authors point out either early (up to 90 days) or late side effects. Hematological and non-hematological toxicity of different grades, esophagitis, dysphagia, skin reaction, laryngeal edema, pneumonia, hypothyroidism, and brachial plexus injury are usually reported among others [13, 22–24]. In some cases respiratory-digestive fistulas, esophageal strictures, and life-threatening bleeding appear [12]. Such complications require urgent tracheotomies, bougienage, esophageal stenting, and gastrostomies [11, 12, 25, 26]. In the late period (median 33.5 mo) there may be cardio-vascular complications such as arrhythmias, ischemic cardiac disease, whereas their cumulative risk within 5 years may reach 17.5 % [22]. The rate of CRT complications may reach 36.9 % resulting in 2.2 % of mortality [9]. Some authors announced mortality of higher rate 4.3 % [13]. What is more important, some authors, specifically, Valmasoni et al., (2018) declared that 29 of 92 patients (31.5 %) had undergone salvage surgery for partially or non-responded tumors.

Thereafter, we can hardly consider concurrent CRT to be a safe alternative to surgery. This modality is not less aggressive; it has its own set of side effects and complications, including lethal ones. In the light of this, functional outcomes may be unsatisfactory.

We suppose development of early and late surgical and post-CRT complications contribute to hazard risk function acceleration within the first year of surveillance. Some authors reckon as well that treatment complications adversely affect OS [17].

We believe surgery and CRT should not be thought as competitive modes, and their reasonable successive combination may be a rational approach. There are 14 subgroups of surgical patients in the present review, and in all cases surgery was coupled with RT or/and CRT. On the other hand, many authors agree that tumor response to CRT is a predictor of OS [9, 11, 13]. Valmasoni et al. (2018) demonstrated that surgery deteriorates long-term results if it was performed after complete tumor response. To the contrary, if surgery is undertaken for partially or non-responding tumors (PR, SD, PD) it has substantial advantages. Gkika et al. (2014) reached a similar inference. Their patients who completely responded to CRT had significantly better (p<0,001) 3-year OS, moreover none of them required salvage surgery. Hence, a choice of treatment mode based on the tumor response to induction therapy may be a rational. In this regard, the contribution of Nakata et al. (2017) referring to chemoselection of patients with CEC may be of interest [30]. Those patients who responded to induction chemotherapy become candidates for CRT. In non-responders surgery is expected to be a more perspective modality in terms of OS. Such an approach is believed to require further investigation. Firstly, similar studies dedicated to chemoselection for CEC are not numerous. Secondly, for patients with other tumors localization who responded to neoadjuvant chemotherapy it is surgery that is really promising. Thirdly, salvage surgery may become more warranted as it either could prolong a patient's life in the case of tumor recurrence or remains a non-competitive option in terms of disability.

Conclusion

In treatment of CEC CRT and surgery are followed by comparable overall survival. These modalities are evenly associated with posterior side effects and complications, which adversely affect functional outcomes and survival. The choice of a treatment mode may depend on tumor response to induction therapy. The latter demands further investigations.

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