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A review of recent treatment trends of laryngeal cancer in Poland.

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Title: A review of recent treatment trends of laryngeal cancer in Poland.

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Objectives: To investigate the utilization of different treatment modalities for patients with laryngeal cancer (LC) during last decade in Poland.

Setting: Retrospective population-based study

Participants: Patients with LC treated between January 2009 and December 2018.

Primary and secondary outcome measures: The contemporary utilisation of treatment modalities of LC: surgery with intent of radical resection (total or partial laryngectomy), radiotherapy (RT) and chemoradiotherapy (CRT).

Results: There was determined the overall number of 22 957 new diagnosis of LC from 2010 to 2018 and confirmed the steady decrease in the incidence rate of LC in following years from 7.7 to 6.03. The mean age of patients with LC was raising by an average of 0.3832 of year per year. There was observed decrease in number of total laryngectomies in subsequent years (from 1122 in 2009 to 776 in 2018). The number of procedures involving partial laryngeal resection was within stable ranges however the upward trend was observed separately for vocal cordectomy. There was established decreased involvement of surgery in LC treatment from 52.8% in 2009 to 24.3% in 2016 with the subsequent rise to 33.7% in 2018. The percentage of patients receiving RT increased from 23.8% in 2009 to 42.1% in 2013 with the next decrease to 25.7% in 2018. The utilization of CRT in LC treatment was progressively increasing over analyzed years from 23.4% in 2009 reaching 40.6% in 2018.

Conclusions: The presented data revealed an increase in total number of organs preserving treatment modality with CRT in subsequent years with decreasing number of total laryngectomies in Polish patients with LC.

Key words: laryngeal cancer, surgery, radiation, chemoradiotherapy

Strengths and limitations of the study

- This study is based on the national cohort of patients with laryngeal cancer.
- It investigates the trends in treatment modalities during the last decade in the presence of the overall decline in outcomes.
- Comparison of organs preserving treatment modality with chemoradiotherapy and surgical procedure of total laryngectomy was analyzed in subsequent years.
- The percentage of transoral laryngeal procedures and open partial laryngectomies was analyzed.

- Information concerning stage, locoregional control, metastatic disease, prior or concurrent cancer diagnosis, received radiation doses, data regarding CT administration with a number of cycles, specific agents, doses and long-term toxicities were not analyzed

Introduction

Approximately 177,422 new cases of laryngeal cancer (LC) were diagnosed worldwide in 2018 according to the estimation of the International Agency for Research on Cancer and the forecasts indicate an increasing trend in the future. In 2017, population-based studies prepared by the Polish National Cancer Registry confirmed 2,224 new cases of LC and 1,580 deaths due to this type of cancer [2]. For comparison, the incidence and mortality due to LC reported in 2009 was 2,413 and 1,585 respectively [3]. Although statistics show decreasing rates for new diagnoses in our country, survival rates are not improving. Recommendations for primary treatment of LC differ depending on the stage of the disease and the site of cancer within the organ but also follow certain trends that promote organ preservation methods and depend on the availability of equipment. Historically, total laryngectomy with postoperative radiation was standard treatment for advanced stage (T3, T4) LC. However, the results of the Department of Veterans Affairs (VA) Laryngeal Cancer Study from 1991 and the Radiation Therapy Oncology Group (RTOG) 91-11 Study from 2003 modified the treatment paradigm focusing on conservative laryngeal therapy with chemoradiation (CRT), primarily in the United States and subsequently in Europe [4,5]. This approach has influenced the management of advanced LC and the number of primary laryngectomies, thus rendering the procedure rescue treatment. For T3 and T4 LC, current treatment protocols recommend concomitant or sequential radiotherapy (RT) with chemotherapy (CT) or total laryngectomy (TL). However, the radiological evidence of cartilage tumor infiltration is rather an indication for surgical resection [6]. In contrast, the early stages of LC (T1 and T2) should always be treated with an initial intent of organ preservation. The recommendations include surgical resection or primary RT and both methods give comparable oncological outcomes. Both these treatment modalities have evolved significantly over the last two decades. The prevalence and advances in transoral endoscopic surgical methods have replaced the open laryngeal surgery in primary treatment of T1 and T2 LC. The improvements in radiation techniques have also reduced the contribution of upfront RT treatment and provided high-quality design and delivery with target volume determination and the use of Intensity Modulated Radiation Therapy – IMRT [7]. This increases the therapeutic dose within the tumor while optimally sparing normal tissue adjacent to the tumor, e.g. the carotid arteries.

The purpose of this study was to investigate the trends in treatment modalities during the last decade in patients with LC in Poland, based on the national cohort of patients from the National Health Fund Database in order to evaluate the findings, compare them with global trends and assess the possibilities for improving survival rates.

Materials and Methods

Patients and Public Involvement statement

Patients were not involved in the study. All data used in the study proposals were de-identified and therefore the approval of the Institutional Review Board was waived. The study protocol is conformed to the principles embodied in the Declaration of Helsinki.

The study design was a retrospective population-based study. The data concerned patients with LC and their treatment procedures between January 2009 and December 2018 and was obtained from the National Database of Hospitalized Patients maintained by the National Health Fund (NFZ) of Poland [8]. The database compiles all data related to hospitalizations in public and private hospitals financed from public sources. The available database contains medical data (including diagnoses and procedures), identification numbers, dates of birth, area codes, and patient genders. Diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10), while surgical procedures are coded using the International Classification of Diseases, 9th Revision (ICD-9).

Patients with laryngeal carcinoma were identified according to the ICD-10 classification with the following codes: C32 - Malignant neoplasm of larynx, C32.0 – Malignant neoplasm of glottis, C32.1 - Malignant neoplasm of supraglottis, C32.2 - Malignant neoplasm of subglottis, C32.3 - Malignant neoplasm of laryngeal cartilage, C32.8 - Malignant neoplasm of overlapping sites of larynx, C32.9 - Malignant neoplasm of larynx, unspecified, C10.1 - Malignant neoplasm of anterior surface of epiglottis, and C13.1 - Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect. Procedures of interest included surgical resection of different extent according to the ICD-9 classification. All of the following procedures were included in the analysis: 30.1 Hemilaryngectomy, 30.2 Other partial laryngectomy, 30.21 Epiglottidectomy, 30.22 Vocal cordectomy, 30.23 Partial laryngectomy with reconstruction, 30.24 Laryngeal cartilage resection, 30.29 Other partial laryngectomy, 30.3 Complete laryngectomy, 30.31 En bloc laryngeal resection with thyroidectomy and tracheostomy, 30.32 Laryngopharyngectomy, 30.39 Other complete laryngectomy, 30.4 Radical laryngectomy (with radical neck dissection), 30.41 Radical laryngectomy (with radical neck dissection) and with thyroidectomy and tracheostomy, 30.49 Other radical laryngectomy, 30.0 Excision or destruction of lesion or tissue of larynx, 30.09 Other excision or destruction of lesion or tissue of larynx, 31.5 Local excision or destruction of larynx lesion or tissue of trachea. The RT and CT treatment was identified according to the ICD-10 classification (Z51.0 - antineoplastic radiation therapy and Z51.1 - antineoplastic chemotherapy).

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Data on the population of Polish citizens were obtained from Statistics Poland (Główny Urząd Statystyczny) [9].

Taking into account different treatment modalities for LC, the following three options were analysed: surgery with intent of radical resection of LC (total or partial laryngectomy) including patients who received induction CRT or adjuvant RT/CRT; radiotherapy - including patients treated with RT alone or following induction CT; and chemoradiotherapy - including patients treated with CRT alone or following induction CT.

Statistical analysis

Python 3.3.6 and Microsoft Excel 2016 were used to separate and analyze patient data from datasets. For quantitative variables, basic statistics (mean and standard deviation) were calculated. A linear regression model was used to analyze age variability of patients. The incidence rate is the number of new cases divided by 100,000 citizens.

Results

Considering the selected ICD-10 codes, the overall number of 61,571 hospitalizations related to LC from 2009 to 2018 in Poland was identified. The number of hospitalizations per year ranged from 5,763 to 6,674 without any specified trend. The highest numbers of hospital stays were recorded for C32.0 (24,208) as well as C32.8 and C32.9 (13,068 and 17,268 respectively). Taking into account only primary hospitalization and the determination of the LC diagnosis, the overall number of 22,957 new diagnoses of LC from 2010 to 2018 was determined. This number could not be established for 2009 year due to incomplete data in the register for previous years and the possibility of revaluation. A steady decrease in the incidence rate of LC was observed in the following years from 7.7 to 6.03 (mean incidence rate 6.63). The trend was especially significant for male patients (the decrease in new diagnoses from 2,577 in 2010 to 1,987 in 2018) but was not as evident for female patients (from 388 in 2010 to 330 in 2018). In contrast to the incidence rate, the mean age of patients with diagnosed LC significantly increased, growing on average by 0.3832 years per year. The trend was described by means of linear regression using the following formula: $Y = 0.3832 * X + 61.345$, where X is the serial number of the year (i.e. 2009 - 1, 2010 - 2 etc.). The regression model was very well fitted to the data and explained 99% ($R^2 = 0.9909$) of age variability of patients. Demographic data on population revealed that about 70% of the LC patients were urban dwellers. The percentage of urban dwellers has slightly decreased over the last 10 years. Table 1.

Table 1. The demographical characteristic of patients with new diagnosis of laryngeal cancer in Polish population from 2010 to 2018.

C32 patient s	2010	2011	2012	2013	2014	2015	2016	2017	2018	All
No of patient s	2965	2682	2653	2571	2520	2539	2360	2350	2317	22957
Populat ion (in thousa nds)	38517	38526	38534	38502	38484	38455	38427	38422	38413	-
Inciden ce rate*	7.70	6.96	6.88	6.68	6.55	6.60	6.14	6.12	6.03	-
Age mean ± SE	62.33 ± 9.43	62.72 ± 9.27	62.72 ± 9.19	63.42 ± 9.13	63.56 ± 8.87	64.1 ± 8.72	64.05 ± 8.99	64.49 ± 8.99	64.82 ± 8.97	63.58 ± 9.06
Women (%)	388 (13.09 %)	336 (12.53 %)	351 (13.23 %)	364 (14.16 %)	351 (13.93 %)	353 (13.9 %)	330 (13.98 %)	308 (13.11 %)	330 (14.24 %)	3111 (13.57 %)
Men (%)	2577 (86.91 %)	2346 (87.47 %)	2302 (86.77 %)	2207 (85.84 %)	2169 (86.07 %)	2186 (86.10 %)	2030 (86.02 %)	2042 (86.89 %)	1987 (85.76 %)	19846 (86.43 %)
Urban residen ce (%)	2184 (73.66 %)	1940 (72.33 %)	1913 (72.11 %)	1868 (72.66 %)	1802 (71.51 %)	1822 (71.76 %)	1672 (70.85 %)	1666 (70.89 %)	1617 (69.79 %)	16484 (71.73 %)
Rural Resista nce (%)	781 (26.34 %)	742 (27.67 %)	740 (27.89 %)	703 (27.34 %)	718 (28.49 %)	717 (28.24 %)	688 (29.15 %)	684 (29.11 %)	700 (30.21 %)	6473 (28.27 %)

*Incidence rate = no of new diagnoses / 100 000 citizens

Analyzing the number of individual ICD-10 codes related to newly diagnosed LC, the highest number of patients with C32.0 (12,566) was identified. A relatively high number of C32.9 and C32 codes were found (5,686 and 1,118 respectively), however neither of them specifies laryngeal location or cancer stage. The new diagnosis of advanced cancer stages with cartilage infiltration C32.3 and extralaryngeal invasion C32.8 were recognized in 286 and 5,279 patients respectively. The calculated total hospitalization coefficient (number of hospitalizations / number of new diagnoses) for LC patients was 2.04 during the analyzed period. Patients with C32.9 were hospitalized most frequently, on average 2.74 hospitalizations.

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The surgical procedures applied to laryngeal cancer treatment were categorized according to the extent of the resection. Procedures involving total laryngectomy (30.3, 30.31, 30.32, 30.39, 30.4, 30.41, 30.49) were performed in 9,562 patients during the 10-year period. The most common procedure was 30.32 – 5,234 (54.7%) and the second in order 30.39 – 2,454 (25.7%). The partial resection of the larynx (30.1, 30.2, 30.21, 30.22, 30.23, 30.24, 30.29) was applied 5,681 times as surgical treatment method over this time with significant advantage of the 30.22 procedure performed 3,182 times (56%). The overall number of procedures restricted to local excision or destruction of the laryngeal lesion (30.0, 30.09, 31.5) was 2,696. Table 2. The number of total laryngectomies decreased in subsequent analyzed years (from 1,122 in 2009 to 776 in 2018). Contrary to total laryngectomy, the number of procedures involving partial laryngeal resection was quite stable in total count with 561 procedures in 2009 and 579 in 2018. However, the upward trend was observed separately for 30.22 procedure (from 250 in 2009 to 393 in 2018) at the cost of a downward trend for other procedures of partial laryngeal resection. Figure 1.

Table 2. The number of surgical procedures according to ICD 9 codes applied to patients with laryngeal cancer during the 10 year period.

ICD9/Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Procedures involving total laryngectomies											
30.3 Complete laryngectomy	4	9	5	6	7	13	24	5	-	-	73
30.31 En bloc laryngeal resection with thyroidectomy and tracheostomy	85	70	39	79	48	33	27	20	15	14	430
30.32 Laryngopharyngectomy	521	472	470	517	539	527	559	547	551	531	5234
30.39 Other complete laryngectomy	347	351	245	303	241	221	202	203	188	153	2454
30.4 Radical laryngectomy (with radical neck dissection)	23	17	8	3	4	6	7	1	-	-	69
30.41 Radical laryngectomy (with radical neck dissection) and with	44	45	31	35	38	45	48	42	39	40	407

thyroidectomy and tracheostomy											
30.49 Other radical laryngectomy	98	96	115	109	108	113	81	67	70	38	895
Summary	1122	1060	913	1052	985	958	948	885	863	776	9562
Procedures involving partial resection of larynx											
30.1 Hemilaryngectomy	42	38	38	25	24	16	16	13	12	13	237
30.2 Other partial laryngectomy	-	3	2	-	-	1	-	-	-	-	6
30.21 Epiglottidectomy	15	11	7	10	10	6	10	5	1	6	81
30.22 Vocal cordectomy	250	276	262	307	249	309	358	369	409	393	3182
30.23 Partial laryngectomy with reconstruction	133	115	94	108	134	93	80	65	57	56	935
30.24 Laryngeal cartilage resection	1	1	1	1	1		3		2	2	12
30.29 Other partial laryngectomy	120	110	120	128	126	152	140	122	101	109	1228
Summary	561	554	524	579	544	577	607	574	582	579	5681
Procedures involving local destruction or excision of laryngeal tissue											
30.0 Excision or destruction of lesion or tissue of larynx	26	6	3	4	1	5	5	-	-	-	50
30.09 Other excision or destruction of lesion or tissue of larynx	161	167	165	176	151	165	210	167	123	186	1671
31.5 Local excision or destruction of larynx lesion or tissue of trachea	46	80	61	67	87	135	123	135	104	137	975

Summary	233	253	229	247	239	305	338	302	227	323	2696
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Considering the surgical procedures with the intent of radical resection of LC (total or partial laryngectomy), they were applied 15,243 times as a treatment modality over the analyzed period. Among those cases the additional treatment of RT or CRT was performed in 4,250 patients. RT alone or with induction CT was applied over the same period for 16,308 patients, while concurrent or subsequent CRT was administered for treatment in 15,032 patients. There was observed a downward trend for surgical methods of LC treatment from 52.8% in 2009 to 24.3% in 2016 with the subsequent rise to 33.7% in 2018. The percentage of patients receiving RT was increasing from 23.8% in 2009 to 42.1% in 2013 and next it decreased to the level of 25.7% in 2018. The utilization of CRT in LC treatment was progressively increasing over analyzed years from 23.4% in 2009 reaching 40.6% in 2018. Table 3. Figure 2.

Table 3. The numbers of different treatment modalities for laryngeal cancer including surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in 2009-2018 with the percentage share in following years.

TREATEMENT \ YEAR	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
SURGERY	1344	1278	1023	1109	998	1044	1073	1040	1005	1042	10956
SURGERY_RT/CRT	339	336	414	522	531	491	482	419	440	313	4287
RT	720	850	1181	1508	1929	2070	2095	2043	1568	960	14924
CT_RT	39	60	92	110	180	191	223	261	152	76	1384
CT_CRT	76	118	174	219	240	301	392	477	352	304	2653
CRT	671	806	990	1102	1125	1401	1622	1766	1568	1328	12379
SURGERY	1683	1614	1437	1631	1529	1535	1555	1459	1445	1355	15243
RT	759	910	1273	1618	2109	2261	2318	2304	1720	1036	16308
CRT	747	924	1164	1321	1365	1702	2014	2243	1920	1632	15032

SURGERY (%)	52.7 8	46.8 1	37.0 9	35.6 9	30.5 6	27.9 2	26.4 1	24.2 9	28.4 2	33.6 8	32.7 2
RT (%)	23.8 0	26.3 9	32.8 6	35.4 0	42.1 5	41.1 2	39.3 7	38.3 6	33.8 2	25.7 5	35.0 1
CRT (%)	23.4 2	26.8 0	30.0 5	28.9 1	27.2 8	30.9 6	34.2 1	37.3 5	37.7 6	40.5 7	32.2 7

SURGERY = SURGERY + SURGERY_RT/CRT; RT = RT + CT_RT; CRT = CT_CRT + CRT

Discussion

The population-based analyses in the majority of developed countries show a decreasing incidence of LC, but paradoxically declining outcomes can be observed over the recent decade. This contradicts trends in survival for other cancer types. It was speculated that the overall decline in outcomes may reflect the consistent rise in larynx-preserving treatment methods with CRT, especially for T4 tumours or partial laryngectomies for T3 [10,11]. The extensive surgical treatment provided satisfactory survival results, however, it induced the deprivation of laryngeal phonation and permanent cervical stoma. The trend of organ-preserving treatment made the selection of treatment for the same tumor far more complex and the fact that it involved opposite strategies, has risen many controversies. The new directions are inevitable, however, their efficiency should be monitored.

The national cohort studies analyzing the contemporary utilisation of treatment modalities of LC confronted to population-based studies are not so commonly performed. However, those expertise can update current trends in practice patterns and asses how the practice affects survival outcomes.

The presented study used the national cohort of patients who were diagnosed and treated between 2009 and 2018 in Poland to measure utilisation trends of LC treatment over that period. Initially, our data confirmed the decrease in the number of patients with LC observed worldwide. In the following years, a steady decrease was observed in the incidence rate from 7.77 / 100,000 in 2009 and 6.03 / 100,000 in 2018. The reports from Germany, the Netherlands, the USA and the Scandinavian countries present such downward trends, however the incidence rates in those countries are lower than in Poland [12-14]. Another aspect to consider after our analysis is the gradual increase in the average age of patients with laryngeal cancer. We observed that the average age of the patients was almost 4 years higher in 2018 compared to 2009. This trend may result from changes in the structure of Polish society but also more effective methods of diagnosis and treatment in the last years. Similar results were presented in the study of Reizenstein et al. [15] or Peller et al. [16], although the increase of average age in German or Swedish patients was not as significant as in Polish ones. Considering the inhabitancy of LC patients almost 72% of them lived in cities, however the percentage decreased over

10 years. The results of the study by Włodarczyk et al. confirm the higher percentage of regular smokers in urban areas (30,3%) than in the countryside (25.4%) [17].

Regarding the surgical treatment methods, a downward trend in total laryngectomies in the subsequent analysed years (from 1,122 in 2009 down to 776 in 2018) could be observed and the declining trend was not only dependent on the decreasing incidence. Contrary to a total laryngectomy, the number of procedures involving partial laryngeal resection remained stable. However an upward trend was observed for vocal cordectomy, performed as transoral laryngeal microsurgery. Hence the open partial laryngectomies rate has decreased. Summarising the overall number of surgical approaches in LC treatment, we observed a temporary downward trend from 52.8% in 2009 to 24.3% in 2016 and subsequent rise to 33.7% in 2018. Contrary to surgery the percentage of patients receiving RT increased from 23.8% in 2009 to 42.1% in 2013 and then there was a decrease to the level of 25.7% in 2018. The utilisation of CRT in LC treatment was increasing progressively over the analysed period from 23.4% in 2009 to 40.6% in 2018. A quite comparable utility of treatment modalities in LC, additionally covering the earlier period is presented by Patel et al. in their analysis of the US National Cancer Database [18]. Their study involved 8,703 patients with stage III/IV LC treated between 2003 and 2011 and revealed the decline in total laryngectomies between 2003 and 2007 from 36.0% to 24.6%; in 2008, the utilisation of total laryngectomies increased to 27.8%, and remained within the range of 26.6% to 31.0% [18]. The use of open partial laryngectomies decreased from a peak incidence of 17.1% in 2003 and remained stable in the range of 9.0% to 10.4% up to 2011. The data presented show an evident rise in larynx-preserving CRT from 47% in 2003 to 61.5% in 2011 [18]. The review of Garcia Lorenzo et al. presents another similar comparison of treatment options offered to patients with T3 and T4 laryngeal cancer over the last 30 years, however from single institution in Spain [19]. They found out the surgery and RT were progressively substituted by CRT in chronological periods of 1985-1994, 1995-2004 and 2005-2014. The participation of surgery in treatment of LC patients declined from 62.5% to 52.2% and 50.5% respectively, while the percentages for RT were 33.5%, 39.7% and 16.8%, respectively. The contribution of CRT has risen from 0% to 8.1% and 32.7%, respectively. Moreover, the authors showed no significant differences in survival depending on treatment for T3 cancer patients, however, there was a significantly higher cancer-specific survival for T4 cancer patients treated surgically. The results of their report revealed the highest survival for patients from 1995 -2004 period and the lowest survival for those treated in the period of 2005–2014 [19]. The results of a recent meta-analysis by Tang et al. that include controlled trials and compare long-term survival, support total laryngectomy for patients with T4 LC and deny the advantage of primary organ preservation treatment for both T3 and T4 LC in increasing the overall survival rate [20]. Therefore, a treatment modality for advanced stages of LC should be addressed especially for further prospective studies. The other reason responsible for declining outcomes of LC that needs to be considered is the increasing age of patients at the primary diagnosis. With the shift of

the average age, the presence of other comorbidities is also inevitable and may not only influence the survival but make some patients susceptible to specific therapy options.

Regarding the treatment modality for T1 stage of LC in retrospective reports, there is a relative equivalence of RT and transoral endoscopic microsurgery and the rates of local control exceed 90% [7]. However for T2 LC the rates decrease significantly and range between 70 and 80%, regardless of treatment approach [21]. Since the oncological benefits are comparable, both methods are verified in terms of voice and swallow outcomes, costs, side effects, time consumption, future options. The technological progress enabled the development of both methods in recent decades. The progress in visualization techniques and widespread adoption of laser techniques in laryngeal microsurgery contribute to increased numbers of CO2 laser endoscopic laryngeal resections of cancer, especially vocal cordectomies. We did not find the data directly analysing the increase in the utility of transoral procedures performed with the laser compared to cold instruments and open partial laryngectomies in glottic cancer. However, Mendelsohn et al. identified a substantial annual growth rates and correct growth rates in original studies covering glottic cancer and laryngeal cancer in the time following the European Laryngological Society classification of cordectomies in 2000 [22]. Unfortunately, the ICD-9 classification does not include specification of the 30.22 procedure regarding involvement of laser versus cold instruments. However according to worldwide trends, we assume that the increase of vocal cordectomies in Poland is inevitably correlated with widespread CO2 laser endoscopic laryngeal microsurgery. The main advantages of laser-assisted LC treatment in comparison to RT are the short time of therapy, decreased costs, the possibility of revising endoscopic resection in case of persistence or recurrence and avoidance of the long-term side effects of RT.

In parallel to laser cordectomies, the new radiation techniques, including IMRT and stereotactic radiation therapy, are verified in studies dedicated to early stages of LC with analysis of sufficient doses (total dose and a single dose/fraction) and addition of sensitising CT [23].

There are limitations to our analysis, resulting mainly from the fact that the National Foundation Database is unfortunately not combined with the National Cancer Registry. Therefore the identification of LC stage with TNM was not possible due to access to ICD-10 diagnosis solely. Information concerning locoregional control, metastatic disease, prior or concurrent cancer diagnosis, received radiation doses, data regarding CT administration with a number of cycles, specific agents, doses and long-term toxicities is also missing.

Conclusions

The presented data revealed an increase in the total number of organ-preserving treatment modality with CRT in the subsequent years and a decreasing number of total laryngectomies in Polish patients with LC. The progressing age of LC onset in Polish population may contribute to declining outcomes.

The multicenter prospective randomised studies comparing treatment modalities should be planned to verify the oncological outcomes and to refer them to patients' needs and cost-effectiveness.

Declarations:

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Figure legends:

Figure 1. Different surgical procedures involving total laryngectomy, partial resection of the larynx or local destruction or excision applied to patients with laryngeal cancer in 2009-2018.

Figure 2. The proportional utilization of surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in treatment of laryngeal cancer in Poland in 2009-2018.

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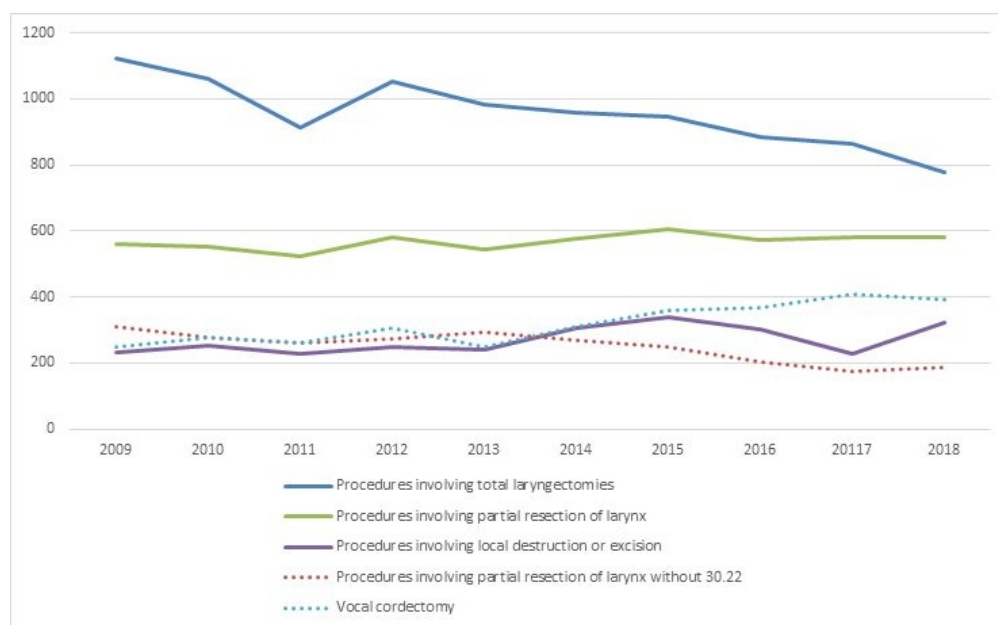


Figure 1. Different surgical procedures involving total laryngectomy, partial resection of the larynx or local destruction or excision applied to patients with laryngeal cancer in 2009-2018.

260x161mm (72 x 72 DPI)

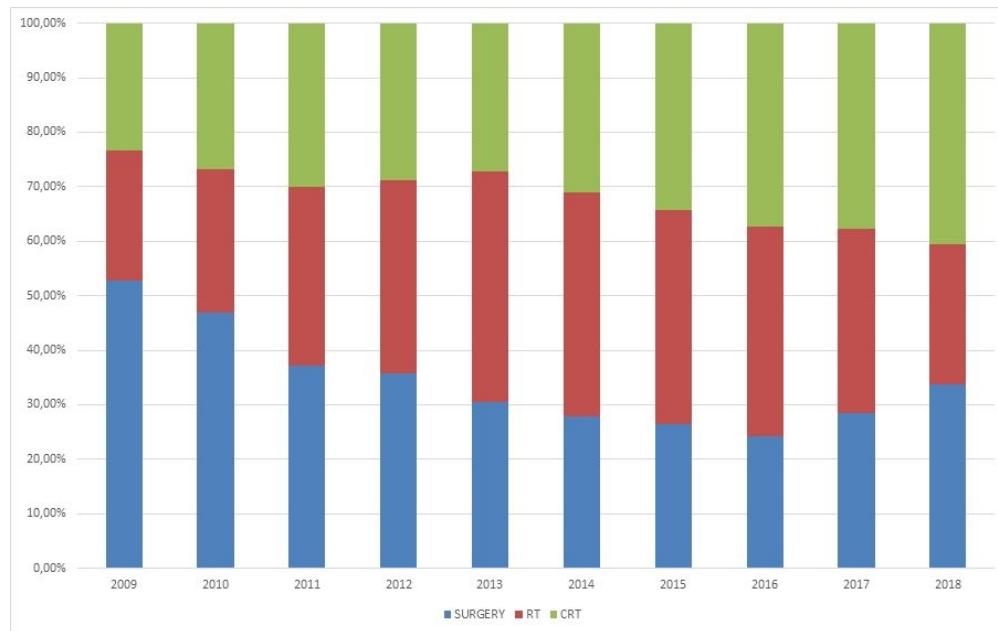


Figure 2. The proportional utilization of surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in treatment of laryngeal cancer in Poland in 2009-2018.

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A review of recent treatment trends of laryngeal cancer in Poland: population-based study.

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Title: A review of recent treatment trends of laryngeal cancer in Poland: population-based study.

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Objectives: To investigate the utilization of different treatment modalities for patients with laryngeal cancer (LC) during last decade in Poland.

Setting: Retrospective population-based study

Participants: Patients with LC treated between January 2009 and December 2018.

Primary and secondary outcome measures: The contemporary utilisation of treatment modalities of LC: surgery with intent of radical resection (total or partial laryngectomy), radiotherapy (RT) and chemoradiotherapy (CRT).

Results: There was determined the overall number of 22 957 new diagnosis of LC from 2010 to 2018 and confirmed the steady decrease in the incidence rate of LC in following years from 7.7 to 6.03. The mean age of patients with LC was raising by an average of 0.3832 of year per year. There was observed decrease in number of total laryngectomies in subsequent years (from 1122 in 2009 to 776 in 2018). The number of procedures involving partial laryngeal resection was within stable ranges however the upward trend was observed separately for vocal cordectomy. There was established decreased involvement of surgery in LC treatment from 52.8% in 2009 to 24.3% in 2016 with the subsequent rise to 33.7% in 2018. The percentage of patients receiving RT increased from 23.8% in 2009 to 42.1% in 2013 with the next decrease to 25.7% in 2018. The utilization of CRT in LC treatment was progressively increasing over analyzed years from 23.4% in 2009 reaching 40.6% in 2018.

Conclusions: The presented data revealed an increase in total number of organs preserving treatment modality with CRT in subsequent years with decreasing number of total laryngectomies in Polish patients with LC.

Key words: laryngeal cancer, surgery, radiation, chemoradiotherapy

Strengths and limitations of the study

- This study is based on the national cohort of patients with laryngeal cancer.
- It investigates the trends in treatment modalities during the last decade in the presence of the overall decline in outcomes.
- Comparison of organs preserving treatment modality with chemoradiotherapy and surgical procedure of total laryngectomy was analyzed in subsequent years.
- The percentage of transoral laryngeal procedures and open partial laryngectomies was analyzed.

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- Information concerning stage, locoregional control, metastatic disease, prior or concurrent cancer diagnosis, received radiation doses, data regarding CT administration with a number of cycles, specific agents, doses and long-term toxicities were not analyzed

Introduction

Approximately 177,422 new cases of laryngeal cancer (LC) were diagnosed worldwide in 2018 according to the estimation of the International Agency for Research on Cancer and the forecasts indicate an increasing trend in the future [1]. In 2017, population-based studies prepared by the Polish National Cancer Registry confirmed 2,224 new cases of LC and 1,580 deaths due to this type of cancer [2]. For comparison, the incidence and mortality due to LC reported in 2009 was 2,413 and 1,585 respectively [3]. Although statistics show decreasing rates for new diagnoses in our country, survival rates are not improving. Recommendations for primary treatment of LC differ depending on the stage of the disease and the site of cancer within the organ but also follow certain trends that promote organ preservation methods and depend on the availability of equipment. Historically, total laryngectomy with postoperative radiation was standard treatment for advanced stage (T3, T4) LC. However, the results of the Department of Veterans Affairs (VA) Laryngeal Cancer Study from 1991 and the Radiation Therapy Oncology Group (RTOG) 91-11 Study from 2003 modified the treatment paradigm focusing on conservative laryngeal therapy with chemoradiation (CRT), primarily in the United States and subsequently in Europe [4,5]. This approach has influenced the management of advanced LC and the number of primary laryngectomies, thus rendering the procedure rescue treatment. For T3 and T4 LC, current treatment protocols recommend concomitant or sequential radiotherapy (RT) with chemotherapy (CT) or total laryngectomy (TL). However, the radiological evidence of cartilage tumor infiltration is rather an indication for surgical resection [6]. In contrast, the early stages of LC (T1 and T2) should always be treated with an initial intent of organ preservation. The recommendations include surgical resection or primary RT and both methods give comparable oncological outcomes. Both these treatment modalities have evolved significantly over the last two decades. The prevalence and advances in transoral endoscopic surgical methods have replaced the open laryngeal surgery in primary treatment of T1 and T2 LC. The improvements in radiation techniques have also reduced the contribution of upfront RT treatment and provided high-quality design and delivery with target volume determination and the use of Intensity Modulated Radiation Therapy – IMRT [7]. This increases the therapeutic dose within the tumor while optimally sparing normal tissue adjacent to the tumor, e.g. the carotid arteries.

The purpose of this study was to investigate the trends in treatment modalities during the last decade in patients with LC in Poland, based on the national cohort of patients from the National Health Fund Database in order to evaluate the findings, compare them with global trends and assess the possibilities for improving survival rates.

Materials and Methods

Patients and Public Involvement statement

All data used in the study proposals were de-identified and therefore the approval of the Institutional Review Board was waived.

The study design was a retrospective population-based study. The data concerned patients with LC and their treatment procedures between January 2009 and December 2018 and was obtained from the National Database of Hospitalized Patients maintained by the National Health Fund (NFZ) of Poland [8]. The database compiles all data related to hospitalizations in public and private hospitals financed from public sources. The available database contains medical data (including diagnoses and procedures), identification numbers, dates of birth, area codes, and patient genders. Diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10), while surgical procedures are coded using the International Classification of Diseases, 9th Revision (ICD-9).

Patients with laryngeal carcinoma were identified according to the ICD-10 classification with the following codes: C32 - Malignant neoplasm of larynx, C32.0 – Malignant neoplasm of glottis, C32.1 - Malignant neoplasm of supraglottis, C32.2 - Malignant neoplasm of subglottis, C32.3 - Malignant neoplasm of laryngeal cartilage, C32.8 - Malignant neoplasm of overlapping sites of larynx, C32.9 - Malignant neoplasm of larynx, unspecified, C10.1 - Malignant neoplasm of anterior surface of epiglottis, and C13.1 - Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect. Procedures of interest included surgical resection of different extent according to the ICD-9 classification. All of the following procedures were included in the analysis: 30.1 Hemilaryngectomy, 30.2 Other partial laryngectomy, 30.21 Epiglottidectomy, 30.22 Vocal cordectomy, 30.23 Partial laryngectomy with reconstruction, 30.24 Laryngeal cartilage resection, 30.29 Other partial laryngectomy, 30.3 Complete laryngectomy, 30.31 En bloc laryngeal resection with thyroidectomy and tracheostomy, 30.32 Laryngopharyngectomy, 30.39 Other complete laryngectomy, 30.4 Radical laryngectomy (with radical neck dissection), 30.41 Radical laryngectomy (with radical neck dissection) and with thyroidectomy and tracheostomy, 30.49 Other radical laryngectomy, 30.0 Excision or destruction of lesion or tissue of larynx, 30.09 Other excision or destruction of lesion or tissue of larynx, 31.5 Local excision or destruction of larynx lesion or tissue of trachea. The RT and CT treatment was identified according to the ICD-10 classification (Z51.0 - antineoplastic radiation therapy and Z51.1 - antineoplastic chemotherapy).

Data on the population of Polish citizens were obtained from Statistics Poland (Główny Urząd Statystyczny) [9].

Taking into account different treatment modalities for LC, the following three options were analysed: surgery with intent of radical resection of LC (total or partial laryngectomy) including patients who

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received induction CRT or adjuvant RT/CRT; radiotherapy - including patients treated with RT alone or following induction CT; and chemoradiotherapy - including patients treated with CRT alone or following induction CT.

Statistical analysis

Python 3.3.6 and Microsoft Excel 2016 were used to separate and analyze patient data from datasets. For quantitative variables, basic statistics (mean and standard deviation) were calculated. A linear regression model was used to analyze age variability of patients. The incidence rate is the number of new cases divided by 100,000 citizens.

Results

Considering the selected ICD-10 codes, the overall number of 61,571 hospitalizations related to LC from 2009 to 2018 in Poland was identified. The number of hospitalizations per year ranged from 5,763 to 6,674 without any specified trend. The highest numbers of hospital stays were recorded for C32.0 - Malignant neoplasm of glottis (24,208) as well as C32.8 - Malignant neoplasm of overlapping sites of larynx and C32.9 - Malignant neoplasm of larynx, unspecified (13,068 and 17,268 respectively). Taking into account only primary hospitalization and the determination of the LC diagnosis, the overall number of 22,957 new diagnoses of LC from 2010 to 2018 was determined. This number could not be established for 2009 year due to incomplete data in the register for previous years and the possibility of revaluation. A steady decrease in the incidence rate of LC was observed in the following years from 7.7 to 6.03 (mean incidence rate 6.63; 95% CI: 6.23-7.03). The trend was especially significant for male patients (the decrease in new diagnoses from 2,577 in 2010 to 1,987 in 2018) but was not as evident for female patients (from 388 in 2010 to 330 in 2018). In contrast to the incidence rate, the mean age of patients with diagnosed LC significantly increased, growing on average by 0.3832 (95% CI: 0.3381-0.4283) years per year. The trend was described by means of linear regression using the following formula: $Y = 0.3832 * X + 61.345$, where X is the serial number of the year (i.e. 2009 - 1, 2010 - 2 etc.). The regression model was very well fitted to the data and explained 99% ($R^2 = 0.9909$) of age variability of patients. Demographic data on population revealed that about 70% of the LC patients were urban dwellers. The percentage of urban dwellers has slightly decreased over the last 10 years. Table 1.

Table 1. The demographical characteristic of patients with new diagnosis of laryngeal cancer in Polish population from 2010 to 2018.

C32 patient s	2010	2011	2012	2013	2014	2015	2016	2017	2018	All

No of patients	2965	2682	2653	2571	2520	2539	2360	2350	2317	22957
Population (in thousands)	38517	38526	38534	38502	38484	38455	38427	38422	38413	-
Incidence rate*	7.70	6.96	6.88	6.68	6.55	6.60	6.14	6.12	6.03	-
Age mean ± SE	62.33 ± 9.43	62.72 ± 9.27	62.72 ± 9.19	63.42 ± 9.13	63.56 ± 8.87	64.1 ± 8.72	64.05 ± 8.99	64.49 ± 8.99	64.82 ± 8.97	63.58 ± 9.06
Women (%)	388 (13.09 %)	336 (12.53 %)	351 (13.23 %)	364 (14.16 %)	351 (13.93 %)	353 (13.9 %)	330 (13.98 %)	308 (13.11 %)	330 (14.24 %)	3111 (13.57 %)
Men (%)	2577 (86.91 %)	2346 (87.47 %)	2302 (86.77 %)	2207 (85.84 %)	2169 (86.07 %)	2186 (86.10 %)	2030 (86.02 %)	2042 (86.89 %)	1987 (85.76 %)	19846 (86.43 %)
Urban residence (%)	2184 (73.66 %)	1940 (72.33 %)	1913 (72.11 %)	1868 (72.66 %)	1802 (71.51 %)	1822 (71.76 %)	1672 (70.85 %)	1666 (70.89 %)	1617 (69.79 %)	16484 (71.73 %)
Rural Residence (%)	781 (26.34 %)	742 (27.67 %)	740 (27.89 %)	703 (27.34 %)	718 (28.49 %)	717 (28.24 %)	688 (29.15 %)	684 (29.11 %)	700 (30.21 %)	6473 (28.27 %)

*Incidence rate = no of all C32 new diagnoses / 100 000 citizens

Analyzing the number of individual ICD-10 codes related to newly diagnosed LC, the highest number of patients with C32.0 - Malignant neoplasm of glottis (12,566) was identified. A relatively high number of C32.9 - Malignant neoplasm of larynx, unspecified and C32 - Malignant neoplasm of larynx were found (5,686 and 1,118 respectively), however neither of them specifies laryngeal location or cancer stage. The new diagnosis of advanced cancer stages with cartilage infiltration C32.3 and extralaryngeal invasion C32.8 were recognized in 286 and 5,279 patients respectively. The calculated total hospitalization coefficient (number of hospitalizations / number of new diagnoses) for LC patients was 2.04 during the analyzed period. Patients with C32.9 were hospitalized most frequently, on average 2.74 hospitalizations.

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The surgical procedures applied to laryngeal cancer treatment were categorized according to the extent of the resection. Procedures involving total laryngectomy (30.3, 30.31, 30.32, 30.39, 30.4, 30.41, 30.49) were performed in 9,562 patients during the 10-year period. The most common procedure was 30.32 Laryngopharyngectomy– 5,234 (54.7%) and the second in order 30.39 Other complete laryngectomy – 2,454 (25.7%). The partial resection of the larynx (30.1, 30.2, 30.21, 30.22, 30.23, 30.24, 30.29) was applied 5,681 times as surgical treatment method over this time with significant advantage of the 30.22 Vocal cordectomy procedure performed 3,182 times (56%). The overall number of procedures restricted to local excision or destruction of the laryngeal lesion (30.0, 30.09, 31.5) was 2,696. Table 2. The number of total laryngectomies decreased in subsequent analyzed years (from 1,122 in 2009 to 776 in 2018). Contrary to total laryngectomy, the number of procedures involving partial laryngeal resection was quite stable in total count with 561 procedures in 2009 and 579 in 2018. However, the upward trend was observed separately for 30.22 Vocal cordectomy procedure (from 250 in 2009 to 393 in 2018) at the cost of a downward trend for other procedures of partial laryngeal resection. Figure 1.

Table 2. The number of surgical procedures applied to patients with laryngeal cancer with relation to extension of resection during the 10 year period.

Year/No (n)	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Surgical procedures involving total laryngectomy											
(n)	1122	1060	913	1052	985	958	948	885	863	776	9562
Surgical procedures involving partial resection of larynx											
(n)	561	554	524	579	544	577	607	574	582	579	5681
Surgical procedures involving local destruction or excision of laryngeal tissue											
(n)	233	253	229	247	239	305	338	302	227	323	2696

Supplementary file 1. Table 2A The number of surgical procedures according to ICD 9 codes applied to patients with laryngeal cancer during the 10 year period.

Considering the surgical procedures with the intent of radical resection of LC (total or partial laryngectomy), they were applied 15,243 times as a treatment modality over the analyzed period. Among those cases the additional treatment of RT or CRT was performed in 4,250 patients. RT alone or with induction CT was applied over the same period for 16,308 patients, while concurrent or subsequent CRT was administered for treatment in 15,032 patients. There was observed a downward

trend for surgical methods of LC treatment from 52.8% in 2009 to 24.3% in 2016 with the subsequent rise to 33.7% in 2018. The percentage of patients receiving RT was increasing from 23.8% in 2009 to 42.1% in 2013 and next it decreased to the level of 25.7% in 2018. The utilization of CRT in LC treatment was progressively increasing over analyzed years from 23.4% in 2009 reaching 40.6% in 2018. Table 3. Figure 2.

Table 3. The numbers of different treatment modalities for laryngeal cancer including surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in 2009-2018 with the percentage share in following years.

TREATEMENT \ YEAR	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
SURGERY	1344	1278	1023	1109	998	1044	1073	1040	1005	1042	10956
SURGERY_RT/CRT	339	336	414	522	531	491	482	419	440	313	4287
RT	720	850	1181	1508	1929	2070	2095	2043	1568	960	14924
CT_RT	39	60	92	110	180	191	223	261	152	76	1384
CT_CRT	76	118	174	219	240	301	392	477	352	304	2653
CRT	671	806	990	1102	1125	1401	1622	1766	1568	1328	12379
SURGERY	1683	1614	1437	1631	1529	1535	1555	1459	1445	1355	15243
RT	759	910	1273	1618	2109	2261	2318	2304	1720	1036	16308
CRT	747	924	1164	1321	1365	1702	2014	2243	1920	1632	15032
SURGERY (%)	52.78	46.81	37.09	35.69	30.56	27.92	26.41	24.29	28.42	33.68	32.72
RT (%)	23.80	26.39	32.86	35.40	42.15	41.12	39.37	38.36	33.82	25.75	35.01
CRT (%)	23.42	26.80	30.05	28.91	27.28	30.96	34.21	37.35	37.76	40.57	32.27

SURGERY = SURGERY + SURGERY_RT/CRT; RT = RT + CT_RT; CRT = CT_CRT + CRT

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Discussion

The population-based analyses in the majority of developed countries show a decreasing incidence of LC, but paradoxically declining outcomes can be observed over the recent decade. This contradicts trends in survival for other cancer types. It was speculated that the overall decline in outcomes may reflect the consistent rise in larynx-preserving treatment methods with CRT, especially for T4 tumours or partial laryngectomies for T3 [10,11]. The extensive surgical treatment provided satisfactory survival results, however, it induced the deprivation of laryngeal phonation and permanent cervical stoma. The trend of organ-preserving treatment made the selection of treatment for the same tumor far more complex and the fact that it involved opposite strategies, has risen many controversies. The new directions are inevitable, however, their efficiency should be monitored.

The national cohort studies analyzing the contemporary utilisation of treatment modalities of LC confronted to population-based studies are not so commonly performed. However, those expertise can update current trends in practice patterns and assess how the practice affects survival outcomes.

The presented study used the national cohort of patients who were diagnosed and treated between 2009 and 2018 in Poland to measure utilisation trends of LC treatment over that period. Initially, our data confirmed the decrease in the number of patients with LC observed worldwide. In the following years, a steady decrease was observed in the incidence rate from 7.77 / 100,000 in 2009 and 6.03 / 100,000 in 2018. The reports from Germany, the Netherlands, the USA and the Scandinavian countries present such downward trends, however the incidence rates in those countries are lower than in Poland [12-14]. Another aspect to consider after our analysis is the gradual increase in the average age of patients with laryngeal cancer. We observed that the average age of the patients was almost 4 years higher in 2018 compared to 2009. This trend may result from changes in the structure of Polish society but also more effective methods of diagnosis and treatment in the last years. Similar results were presented in the study of Reizenstein et al. [15] or Peller et al. [16], although the increase of average age in German or Swedish patients was not as significant as in Polish ones. Considering the inhabitancy of LC patients almost 72% of them lived in cities, however the percentage decreased over 10 years. The results of the study by Włodarczyk et al. confirm the higher percentage of regular smokers in urban areas (30,3%) than in the countryside (25.4%) [17].

Regarding the surgical treatment methods, a downward trend in total laryngectomies in the subsequent analysed years (from 1,122 in 2009 down to 776 in 2018) could be observed and the declining trend was not only dependent on the decreasing incidence. Contrary to a total laryngectomy, the number of procedures involving partial laryngeal resection remained stable. However an upward trend was observed for vocal cordectomy, performed as transoral laryngeal microsurgery. Hence the open partial laryngectomies rate has decreased. Summarising the overall number of surgical approaches in LC treatment, we observed a temporary downward trend from 52.8% in 2009 to 24.3% in 2016 and

subsequent rise to 33.7% in 2018. Contrary to surgery the percentage of patients receiving RT increased from 23.8% in 2009 to 42.1% in 2013 and then there was a decrease to the level of 25.7% in 2018. The utilisation of CRT in LC treatment was increasing progressively over the analysed period from 23.4% in 2009 to 40.6% in 2018. A quite comparable utility of treatment modalities in LC, additionally covering the earlier period is presented by Patel et al. in their analysis of the US National Cancer Database [18]. Their study involved 8,703 patients with stage III/IV LC treated between 2003 and 2011 and revealed the decline in total laryngectomies between 2003 and 2007 from 36.0% to 24.6%; in 2008, the utilisation of total laryngectomies increased to 27.8%, and remained within the range of 26.6% to 31.0% [18]. The use of open partial laryngectomies decreased from a peak incidence of 17.1% in 2003 and remained stable in the range of 9.0% to 10.4% up to 2011. The data presented show an evident rise in larynx-preserving CRT from 47% in 2003 to 61.5% in 2011 [18]. The review of Garcia Lorenzo et al. presents another similar comparison of treatment options offered to patients with T3 and T4 laryngeal cancer over the last 30 years, however from single institution in Spain [19]. They found out the surgery and RT were progressively substituted by CRT in chronological periods of 1985-1994, 1995-2004 and 2005-2014. The participation of surgery in treatment of LC patients declined from 62.5% to 52.2% and 50.5% respectively, while the percentages for RT were 33.5%, 39.7% and 16.8%, respectively. The contribution of CRT has risen from 0% to 8.1% and 32.7%, respectively. Moreover, the authors showed no significant differences in survival depending on treatment for T3 cancer patients, however, there was a significantly higher cancer-specific survival for T4 cancer patients treated surgically. The results of their report revealed the highest survival for patients from 1995 -2004 period and the lowest survival for those treated in the period of 2005–2014 [19]. The results of a recent meta-analysis by Tang et al. that include controlled trials and compare long-term survival, support total laryngectomy for patients with T4 LC and deny the advantage of primary organ preservation treatment for both T3 and T4 LC in increasing the overall survival rate [20]. Therefore, a treatment modality for advanced stages of LC should be addressed especially for further prospective studies. The other reason responsible for declining outcomes of LC that needs to be considered is the increasing age of patients at the primary diagnosis. With the shift of the average age, the presence of other comorbidities is also inevitable and may not only influence the survival but make some patients susceptible to specific therapy options.

Regarding the treatment modality for T1 stage of LC in retrospective reports, there is a relative equivalence of RT and transoral endoscopic microsurgery and the rates of local control exceed 90% [7]. However for T2 LC the rates decrease significantly and range between 70 and 80%, regardless of treatment approach [21]. Since the oncological benefits are comparable, both methods are verified in terms of voice and swallow outcomes, costs, side effects, time consumption, future options. The technological progress enabled the development of both methods in recent decades. The progress in visualization techniques and widespread adoption of laser techniques in laryngeal microsurgery

contribute to increased numbers of CO₂ laser endoscopic laryngeal resections of cancer, especially vocal cordectomies. We did not find the data directly analysing the increase in the utility of transoral procedures performed with the laser compared to cold instruments and open partial laryngectomies in glottic cancer. However, Mendelsohn et al. identified a substantial annual growth rates and correct growth rates in original studies covering glottic cancer and laryngeal cancer in the time following the European Laryngological Society classification of cordectomies in 2000 [22]. Unfortunately, the ICD-9 classification does not include specification of the 30.22 procedure regarding involvement of laser versus cold instruments. However according to worldwide trends, we assume that the increase of vocal cordectomies in Poland is inevitably correlated with widespread CO₂ laser endoscopic laryngeal microsurgery. The main advantages of laser-assisted LC treatment in comparison to RT are the short time of therapy, decreased costs, the possibility of revising endoscopic resection in case of persistence or recurrence and avoidance of the long-term side effects of RT.

In parallel to laser cordectomies, the new radiation techniques, including IMRT and stereotactic radiation therapy, are verified in studies dedicated to early stages of LC with analysis of sufficient doses (total dose and a single dose/fraction) and addition of sensitising CT [23].

There are limitations to our analysis, resulting mainly from the fact that the National Foundation Database is unfortunately not combined with the National Cancer Registry. Therefore the identification of LC stage with TNM was not possible due to access to ICD-10 diagnosis solely. Information concerning locoregional control, metastatic disease, prior or concurrent cancer diagnosis, received radiation doses, data regarding CT administration with a number of cycles, specific agents, doses and long-term toxicities is also missing.

Conclusions

The presented data revealed an increase in the total number of organ-preserving treatment modality with CRT in the subsequent years and a decreasing number of total laryngectomies in Polish patients with LC. The progressing age of LC onset in Polish population may contribute to declining outcomes. The multicenter prospective randomised studies comparing treatment modalities should be planned to verify the oncological outcomes and to refer them to patients' needs and cost-effectiveness.

Declarations:

Authors' contributions: Rzepakowska A. Conceptualization, methodology, writing, reviewing, editing and visualization. Żurek M: Methodology, data extraction, software and formal analysis, writing – draft, visualization. Niemczyk K. Reviewing, editing.

Conflicts of interest/Competing interests – none declared

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Data sharing statement: Deidentified individual participant data that underlie the results are reported in the article (text, tables, figures and supplementary file).

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Figure legends:

Figure 1. Different surgical procedures involving total laryngectomy, partial resection of the larynx or local destruction or excision applied to patients with laryngeal cancer in 2009-2018.

Figure 2. The proportional utilization of surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in treatment of laryngeal cancer in Poland in 2009-2018.

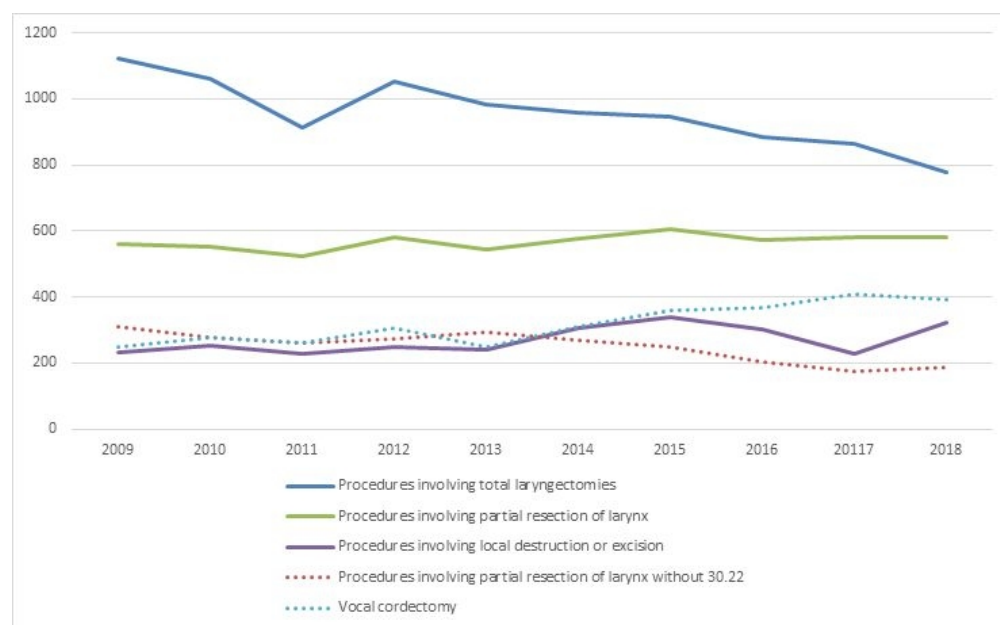


Figure 1. Different surgical procedures involving total laryngectomy, partial resection of the larynx or local destruction or excision applied to patients with laryngeal cancer in 2009-2018.

260x161mm (72 x 72 DPI)

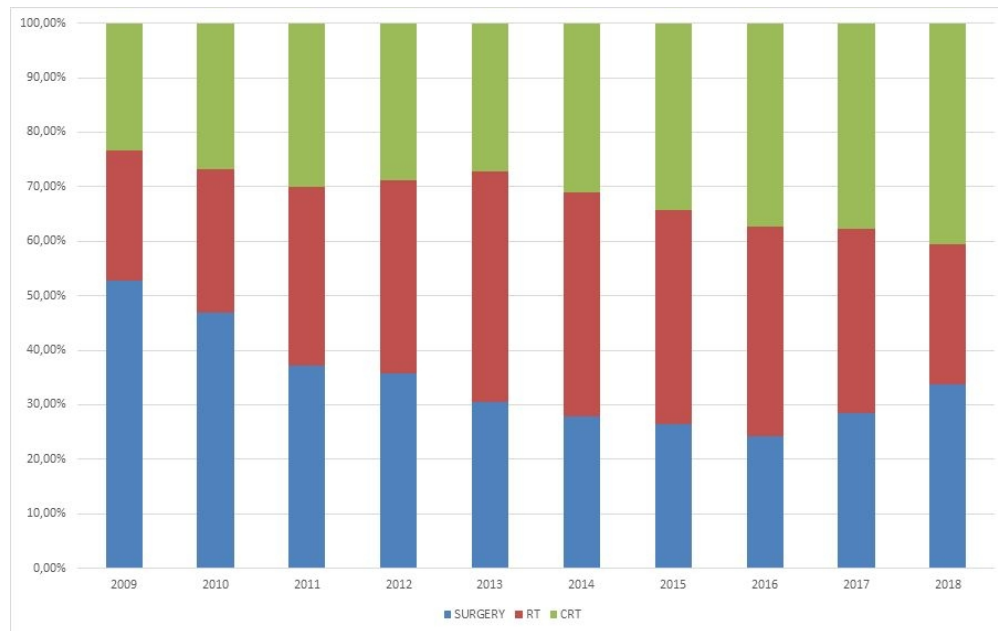


Figure 2. The proportional utilization of surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in treatment of laryngeal cancer in Poland in 2009-2018.

319x201mm (72 x 72 DPI)

Table 2A. The number of surgical procedures according to ICD 9 codes applied to patients with laryngeal cancer during the 10 year period.

ICD9/Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Procedures involving total laryngectomies											
30.3 Complete laryngectomy	4	9	5	6	7	13	24	5	-	-	73
30.31 En bloc laryngeal resection with thyroidectomy and tracheostomy	85	70	39	79	48	33	27	20	15	14	430
30.32 Laryngopharyngectomy	521	472	470	517	539	527	559	547	551	531	5234
30.39 Other complete laryngectomy	347	351	245	303	241	221	202	203	188	153	2454
30.4 Radical laryngectomy (with radical neck dissection)	23	17	8	3	4	6	7	1	-	-	69
30.41 Radical laryngectomy (with radical neck dissection) and with thyroidectomy and tracheostomy	44	45	31	35	38	45	48	42	39	40	407
30.49 Other radical laryngectomy	98	96	115	109	108	113	81	67	70	38	895
Summary	1122	1060	913	1052	985	958	948	885	863	776	9562
Procedures involving partial resection of larynx											
30.1 Hemilaryngectomy	42	38	38	25	24	16	16	13	12	13	237
30.2 Other partial laryngectomy	-	3	2	-	-	1	-	-	-	-	6

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30.21 Epiglottidectomy	15	11	7	10	10	6	10	5	1	6	81
30.22 Vocal cordectomy	250	276	262	307	249	309	358	369	409	393	3182
30.23 Partial laryngectomy with reconstruction	133	115	94	108	134	93	80	65	57	56	935
30.24 Laryngeal cartilage resection	1	1	1	1	1		3		2	2	12
30.29 Other partial laryngectomy	120	110	120	128	126	152	140	122	101	109	1228
Summary	561	554	524	579	544	577	607	574	582	579	5681
Procedures involving local destruction or excision of laryngeal tissue											
30.0 Excision or destruction of lesion or tissue of larynx	26	6	3	4	1	5	5	-	-	-	50
30.09 Other excision or destruction of lesion or tissue of larynx	161	167	165	176	151	165	210	167	123	186	1671
31.5 Local excision or destruction of larynx lesion or tissue of trachea	46	80	61	67	87	135	123	135	104	137	975
Summary	233	253	229	247	239	305	338	302	227	323	2696

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract Title page 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found Abstract page 2, results section
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Throughout the introduction, page 3
Objectives	3	State specific objectives, including any prespecified hypotheses The last paragraph of the introduction, page 3
Methods		
Study design	4	Present key elements of study design early in the paper The last paragraph of the methods section, page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Second paragraph of the methods section, page 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Third paragraph of the methods section, page 4 (b) For matched studies, give matching criteria and number of exposed and unexposed - not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Third paragraph of the methods section, page 4
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - not applicable
Bias	9	Describe any efforts to address potential sources of bias - not applicable
Study size	10	Explain how the study size was arrived at Second paragraph of the methods section, page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Described in statistical analysis subsection, page 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding Described in statistical analysis subsection, page 5 (b) Describe any methods used to examine subgroups and interactions Described in statistical analysis subsection, page 5 (c) Explain how missing data were addressed - not applicable (d) If applicable, explain how loss to follow-up was addressed - not applicable (e) Describe any sensitivity analyses - not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed The result section, page 5, table 1.

		(b) Give reasons for non-participation at each stage - not applicable
		(c) Consider use of a flow diagram - not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Throughout the result section, page 5 -8, table 1, table 2, table 3.
		(b) Indicate number of participants with missing data for each variable of interest - not applicable
		(c) Summarise follow-up time (eg, average and total amount) - not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time - not applicable
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included The results section, page 5, table 1
		(b) Report category boundaries when continuous variables were categorized - not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - not applicable
Discussion		
Key results	18	Summarise key results with reference to study objectives - page 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias The last paragraph of the discussion, page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Throughout the discussion page 9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results - not applicable
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Declarations, page 11-12.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

A review of recent treatment trends of laryngeal cancer in Poland: population-based study.

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Title: A review of recent treatment trends of laryngeal cancer in Poland: population-based study.

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Objectives: To investigate the utilization of different treatment modalities for patients with laryngeal cancer (LC) during last decade in Poland.

Setting: Retrospective population-based study

Participants: Patients with LC treated between January 2009 and December 2018.

Primary and secondary outcome measures: The contemporary utilisation of treatment modalities of LC: surgery with intent of radical resection (total or partial laryngectomy), radiotherapy (RT) and chemoradiotherapy (CRT).

Results: There was determined the overall number of 22 957 new diagnosis of LC from 2010 to 2018 and confirmed the steady decrease in the incidence rate of LC in following years from 7.7 to 6.03. The mean age of patients with LC was raising by an average of 0.3832 of year per year. There was observed decrease in number of total laryngectomies in subsequent years (from 1122 in 2009 to 776 in 2018). The number of procedures involving partial laryngeal resection was within stable ranges however the upward trend was observed separately for vocal cordectomy. There was established decreased involvement of surgery in LC treatment from 52.8% in 2009 to 24.3% in 2016 with the subsequent rise to 33.7% in 2018. The percentage of patients receiving RT increased from 23.8% in 2009 to 42.1% in 2013 with the next decrease to 25.7% in 2018. The utilization of CRT in LC treatment was progressively increasing over analyzed years from 23.4% in 2009 reaching 40.6% in 2018.

Conclusions: The presented data revealed an increase in total number of organs preserving treatment modality with CRT in subsequent years with decreasing number of total laryngectomies in Polish patients with LC.

Key words: laryngeal cancer, surgery, radiation, chemoradiotherapy

Strengths and limitations of the study

- This study is based on the national cohort of patients with laryngeal cancer.
- It investigates the trends in treatment modalities during the last decade in the presence of the overall decline in outcomes.
- Comparison of organs preserving treatment modality with chemoradiotherapy and surgical procedure of total laryngectomy was analyzed in subsequent years.
- The percentage of transoral laryngeal procedures and open partial laryngectomies was analyzed.

- Information concerning stage, locoregional control, metastatic disease, prior or concurrent cancer diagnosis, received radiation doses, data regarding CT administration with a number of cycles, specific agents, doses and long-term toxicities were not analyzed

Introduction

Approximately 177,422 new cases of laryngeal cancer (LC) were diagnosed worldwide in 2018 according to the estimation of the International Agency for Research on Cancer and the forecasts indicate an increasing trend in the future [1]. In 2017, population-based studies prepared by the Polish National Cancer Registry confirmed 2,224 new cases of LC and 1,580 deaths due to this type of cancer [2]. For comparison, the incidence and mortality due to LC reported in 2009 was 2,413 and 1,585 respectively [3]. Although statistics show decreasing rates for new diagnoses in our country, survival rates are not improving. Recommendations for primary treatment of LC differ depending on the stage of the disease and the site of cancer within the organ but also follow certain trends that promote organ preservation methods and depend on the availability of equipment. Historically, total laryngectomy with postoperative radiation was standard treatment for advanced stage (T3, T4) LC. However, the results of the Department of Veterans Affairs (VA) Laryngeal Cancer Study from 1991 and the Radiation Therapy Oncology Group (RTOG) 91-11 Study from 2003 modified the treatment paradigm focusing on conservative laryngeal therapy with chemoradiation (CRT), primarily in the United States and subsequently in Europe [4,5]. This approach has influenced the management of advanced LC and the number of primary laryngectomies, thus rendering the procedure rescue treatment. For T3 and T4 LC, current treatment protocols recommend concomitant or sequential radiotherapy (RT) with chemotherapy (CT) or total laryngectomy (TL). However, the radiological evidence of cartilage tumor infiltration is rather an indication for surgical resection [6]. In contrast, the early stages of LC (T1 and T2) should always be treated with an initial intent of organ preservation. The recommendations include surgical resection or primary RT and both methods give comparable oncological outcomes. Both these treatment modalities have evolved significantly over the last two decades. The prevalence and advances in transoral endoscopic surgical methods have replaced the open laryngeal surgery in primary treatment of T1 and T2 LC. The improvements in radiation techniques have also reduced the contribution of upfront RT treatment and provided high-quality design and delivery with target volume determination and the use of Intensity Modulated Radiation Therapy – IMRT [7]. This increases the therapeutic dose within the tumor while optimally sparing normal tissue adjacent to the tumor, e.g. the carotid arteries.

The purpose of this study was to investigate the trends in treatment modalities during the last decade in patients with LC in Poland, based on the national cohort of patients from the National Health Fund Database in order to evaluate the findings, compare them with global trends and assess the possibilities for improving survival rates.

Materials and Methods

Patients and Public Involvement statement

All data used in the study proposals were de-identified and therefore the approval of the Institutional Review Board was waived. Patients were not involved in the study.

The study design was a retrospective population-based study. The data concerned patients with LC and their treatment procedures between January 2009 and December 2018 and was obtained from the National Database of Hospitalized Patients maintained by the National Health Fund (NFZ) of Poland [8]. The database compiles all data related to hospitalizations in public and private hospitals financed from public sources. The available database contains medical data (including diagnoses and procedures), identification numbers, dates of birth, area codes, and patient genders. Diagnoses are coded according to the International Classification of Diseases, 10th Revision (ICD-10), while surgical procedures are coded using the International Classification of Diseases, 9th Revision (ICD-9).

Patients with laryngeal carcinoma were identified according to the ICD-10 classification with the following codes: C32 - Malignant neoplasm of larynx, C32.0 – Malignant neoplasm of glottis, C32.1 - Malignant neoplasm of supraglottis, C32.2 - Malignant neoplasm of subglottis, C32.3 - Malignant neoplasm of laryngeal cartilage, C32.8 - Malignant neoplasm of overlapping sites of larynx, C32.9 - Malignant neoplasm of larynx, unspecified, C10.1 - Malignant neoplasm of anterior surface of epiglottis, and C13.1 - Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect. Procedures of interest included surgical resection of different extent according to the ICD-9 classification. All of the following procedures were included in the analysis: 30.1 Hemilaryngectomy, 30.2 Other partial laryngectomy, 30.21 Epiglottidectomy, 30.22 Vocal cordectomy, 30.23 Partial laryngectomy with reconstruction, 30.24 Laryngeal cartilage resection, 30.29 Other partial laryngectomy, 30.3 Complete laryngectomy, 30.31 En bloc laryngeal resection with thyroidectomy and tracheostomy, 30.32 Laryngopharyngectomy, 30.39 Other complete laryngectomy, 30.4 Radical laryngectomy (with radical neck dissection), 30.41 Radical laryngectomy (with radical neck dissection) and with thyroidectomy and tracheostomy, 30.49 Other radical laryngectomy, 30.0 Excision or destruction of lesion or tissue of larynx, 30.09 Other excision or destruction of lesion or tissue of larynx, 31.5 Local excision or destruction of larynx lesion or tissue of trachea. The RT and CT treatment was identified according to the ICD-10 classification (Z51.0 - antineoplastic radiation therapy and Z51.1 - antineoplastic chemotherapy).

Data on the population of Polish citizens were obtained from Statistics Poland (Główny Urząd Statystyczny) [9].

Taking into account different treatment modalities for LC, the following three options were analysed: surgery with intent of radical resection of LC (total or partial laryngectomy) including patients who

received induction CRT or adjuvant RT/CRT; radiotherapy - including patients treated with RT alone or following induction CT; and chemoradiotherapy - including patients treated with CRT alone or following induction CT.

Statistical analysis

Python 3.3.6 and Microsoft Excel 2016 were used to separate and analyze patient data from datasets. For quantitative variables, basic statistics (mean and standard deviation) were calculated. A linear regression model was used to analyze age variability of patients. The incidence rate is the number of new cases divided by 100,000 citizens.

Results

Considering the selected ICD-10 codes, the overall number of 61,571 hospitalizations related to LC from 2009 to 2018 in Poland was identified. The number of hospitalizations per year ranged from 5,763 to 6,674 without any specified trend. The highest numbers of hospital stays were recorded for C32.0 - Malignant neoplasm of glottis (24,208) as well as C32.8 - Malignant neoplasm of overlapping sites of larynx and C32.9 - Malignant neoplasm of larynx, unspecified (13,068 and 17,268 respectively). Taking into account only primary hospitalization and the determination of the LC diagnosis, the overall number of 22,957 new diagnoses of LC from 2010 to 2018 was determined. This number could not be established for 2009 year due to incomplete data in the register for previous years and the possibility of revaluation. A steady decrease in the incidence rate of LC was observed in the following years from 7.7 to 6.03 (mean incidence rate 6.63; 95% CI: 6.23-7.03). The trend was especially significant for male patients (the decrease in new diagnoses from 2,577 in 2010 to 1,987 in 2018) but was not as evident for female patients (from 388 in 2010 to 330 in 2018). In contrast to the incidence rate, the mean age of patients with diagnosed LC significantly increased, growing on average by 0.3832 (95% CI: 0.3381-0.4283) years per year. The trend was described by means of linear regression using the following formula: $Y = 0.3832 * X + 61.345$, where X is the serial number of the year (i.e. 2009 - 1, 2010 - 2 etc.). The regression model was very well fitted to the data and explained 99% ($R^2 = 0.9909$) of age variability of patients. Demographic data on population revealed that about 70% of the LC patients were urban dwellers. The percentage of urban dwellers has slightly decreased over the last 10 years. Table 1.

Table 1. The demographical characteristic of patients with new diagnosis of laryngeal cancer in Polish population from 2010 to 2018.

C32 patient s	2010	2011	2012	2013	2014	2015	2016	2017	2018	All

No of patients	2965	2682	2653	2571	2520	2539	2360	2350	2317	22957
Population (in thousands)	38517	38526	38534	38502	38484	38455	38427	38422	38413	-
Incidence rate*	7.70	6.96	6.88	6.68	6.55	6.60	6.14	6.12	6.03	-
Age mean ± SE	62.33 ± 9.43	62.72 ± 9.27	62.72 ± 9.19	63.42 ± 9.13	63.56 ± 8.87	64.1 ± 8.72	64.05 ± 8.99	64.49 ± 8.99	64.82 ± 8.97	63.58 ± 9.06
Women (%)	388 (13.09 %)	336 (12.53 %)	351 (13.23 %)	364 (14.16 %)	351 (13.93 %)	353 (13.9 %)	330 (13.98 %)	308 (13.11 %)	330 (14.24 %)	3111 (13.57 %)
Men (%)	2577 (86.91 %)	2346 (87.47 %)	2302 (86.77 %)	2207 (85.84 %)	2169 (86.07 %)	2186 (86.10 %)	2030 (86.02 %)	2042 (86.89 %)	1987 (85.76 %)	19846 (86.43 %)
Urban residence (%)	2184 (73.66 %)	1940 (72.33 %)	1913 (72.11 %)	1868 (72.66 %)	1802 (71.51 %)	1822 (71.76 %)	1672 (70.85 %)	1666 (70.89 %)	1617 (69.79 %)	16484 (71.73 %)
Rural Residence (%)	781 (26.34 %)	742 (27.67 %)	740 (27.89 %)	703 (27.34 %)	718 (28.49 %)	717 (28.24 %)	688 (29.15 %)	684 (29.11 %)	700 (30.21 %)	6473 (28.27 %)

*Incidence rate = no of all C32 new diagnoses / 100 000 citizens

Analyzing the number of individual ICD-10 codes related to newly diagnosed LC, the highest number of patients with C32.0 - Malignant neoplasm of glottis (12,566) was identified. A relatively high number of C32.9 - Malignant neoplasm of larynx, unspecified and C32 - Malignant neoplasm of larynx were found (5,686 and 1,118 respectively), however neither of them specifies laryngeal location or cancer stage. The new diagnosis of advanced cancer stages with cartilage infiltration C32.3 and extralaryngeal invasion C32.8 were recognized in 286 and 5,279 patients respectively. The calculated total hospitalization coefficient (number of hospitalizations / number of new diagnoses) for LC patients was 2.04 during the analyzed period. Patients with C32.9 were hospitalized most frequently, on average 2.74 hospitalizations.

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The surgical procedures applied to laryngeal cancer treatment were categorized according to the extent of the resection. Procedures involving total laryngectomy (30.3, 30.31, 30.32, 30.39, 30.4, 30.41, 30.49) were performed in 9,562 patients during the 10-year period. The most common procedure was 30.32 Laryngopharyngectomy– 5,234 (54.7%) and the second in order 30.39 Other complete laryngectomy – 2,454 (25.7%). The partial resection of the larynx (30.1, 30.2, 30.21, 30.22, 30.23, 30.24, 30.29) was applied 5,681 times as surgical treatment method over this time with significant advantage of the 30.22 Vocal cordectomy procedure performed 3,182 times (56%). The overall number of procedures restricted to local excision or destruction of the laryngeal lesion (30.0, 30.09, 31.5) was 2,696. Table 2. The number of total laryngectomies decreased in subsequent analyzed years (from 1,122 in 2009 to 776 in 2018). Contrary to total laryngectomy, the number of procedures involving partial laryngeal resection was quite stable in total count with 561 procedures in 2009 and 579 in 2018. However, the upward trend was observed separately for 30.22 Vocal cordectomy procedure (from 250 in 2009 to 393 in 2018) at the cost of a downward trend for other procedures of partial laryngeal resection. Figure 1.

Table 2. The number of surgical procedures applied to patients with laryngeal cancer with relation to extension of resection during the 10 year period.

Year/No (n)	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Surgical procedures involving total laryngectomy											
(n)	1122	1060	913	1052	985	958	948	885	863	776	9562
Surgical procedures involving partial resection of larynx											
(n)	561	554	524	579	544	577	607	574	582	579	5681
Surgical procedures involving local destruction or excision of laryngeal tissue											
(n)	233	253	229	247	239	305	338	302	227	323	2696

Supplementary file 1-Table A. The number of surgical procedures according to ICD 9 codes applied to patients with laryngeal cancer during the 10-year period.

Considering the surgical procedures with the intent of radical resection of LC (total or partial laryngectomy), they were applied 15,243 times as a treatment modality over the analyzed period. Among those cases the additional treatment of RT or CRT was performed in 4,250 patients. RT alone or with induction CT was applied over the same period for 16,308 patients, while concurrent or subsequent CRT was administered for treatment in 15,032 patients. There was observed a downward

trend for surgical methods of LC treatment from 52.8% in 2009 to 24.3% in 2016 with the subsequent rise to 33.7% in 2018. The percentage of patients receiving RT was increasing from 23.8% in 2009 to 42.1% in 2013 and next it decreased to the level of 25.7% in 2018. The utilization of CRT in LC treatment was progressively increasing over analyzed years from 23.4% in 2009 reaching 40.6% in 2018. Table 3. Figure 2.

Table 3. The numbers of different treatment modalities for laryngeal cancer including surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in 2009-2018 with the percentage share in following years.

TREATEMENT \ YEAR	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
SURGERY	1344	1278	1023	1109	998	1044	1073	1040	1005	1042	10956
SURGERY_RT/CRT	339	336	414	522	531	491	482	419	440	313	4287
RT	720	850	1181	1508	1929	2070	2095	2043	1568	960	14924
CT_RT	39	60	92	110	180	191	223	261	152	76	1384
CT_CRT	76	118	174	219	240	301	392	477	352	304	2653
CRT	671	806	990	1102	1125	1401	1622	1766	1568	1328	12379
SURGERY	1683	1614	1437	1631	1529	1535	1555	1459	1445	1355	15243
RT	759	910	1273	1618	2109	2261	2318	2304	1720	1036	16308
CRT	747	924	1164	1321	1365	1702	2014	2243	1920	1632	15032
SURGERY (%)	52.78	46.81	37.09	35.69	30.56	27.92	26.41	24.29	28.42	33.68	32.72
RT (%)	23.80	26.39	32.86	35.40	42.15	41.12	39.37	38.36	33.82	25.75	35.01
CRT (%)	23.42	26.80	30.05	28.91	27.28	30.96	34.21	37.35	37.76	40.57	32.27

SURGERY = SURGERY + SURGERY_RT/CRT; RT = RT + CT_RT; CRT = CT_CRT + CRT

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Discussion

The population-based analyses in the majority of developed countries show a decreasing incidence of LC, but paradoxically declining outcomes can be observed over the recent decade. This contradicts trends in survival for other cancer types. It was speculated that the overall decline in outcomes may reflect the consistent rise in larynx-preserving treatment methods with CRT, especially for T4 tumours or partial laryngectomies for T3 [10,11]. The extensive surgical treatment provided satisfactory survival results, however, it induced the deprivation of laryngeal phonation and permanent cervical stoma. The trend of organ-preserving treatment made the selection of treatment for the same tumor far more complex and the fact that it involved opposite strategies, has risen many controversies. The new directions are inevitable, however, their efficiency should be monitored.

The national cohort studies analyzing the contemporary utilisation of treatment modalities of LC confronted to population-based studies are not so commonly performed. However, those expertise can update current trends in practice patterns and assess how the practice affects survival outcomes.

The presented study used the national cohort of patients who were diagnosed and treated between 2009 and 2018 in Poland to measure utilisation trends of LC treatment over that period. Initially, our data confirmed the decrease in the number of patients with LC observed worldwide. In the following years, a steady decrease was observed in the incidence rate from 7.77 / 100,000 in 2009 and 6.03 / 100,000 in 2018. The reports from Germany, the Netherlands, the USA and the Scandinavian countries present such downward trends, however the incidence rates in those countries are lower than in Poland [12-14]. Another aspect to consider after our analysis is the gradual increase in the average age of patients with laryngeal cancer. We observed that the average age of the patients was almost 4 years higher in 2018 compared to 2009. This trend may result from changes in the structure of Polish society but also more effective methods of diagnosis and treatment in the last years. Similar results were presented in the study of Reizenstein et al. [15] or Peller et al. [16], although the increase of average age in German or Swedish patients was not as significant as in Polish ones. Considering the inhabitancy of LC patients almost 72% of them lived in cities, however the percentage decreased over 10 years. The results of the study by Włodarczyk et al. confirm the higher percentage of regular smokers in urban areas (30,3%) than in the countryside (25.4%) [17].

Regarding the surgical treatment methods, a downward trend in total laryngectomies in the subsequent analysed years (from 1,122 in 2009 down to 776 in 2018) could be observed and the declining trend was not only dependent on the decreasing incidence. Contrary to a total laryngectomy, the number of procedures involving partial laryngeal resection remained stable. However an upward trend was observed for vocal cordectomy, performed as transoral laryngeal microsurgery. Hence the open partial laryngectomies rate has decreased. Summarising the overall number of surgical approaches in LC treatment, we observed a temporary downward trend from 52.8% in 2009 to 24.3% in 2016 and

subsequent rise to 33.7% in 2018. Contrary to surgery the percentage of patients receiving RT increased from 23.8% in 2009 to 42.1% in 2013 and then there was a decrease to the level of 25.7% in 2018. The utilisation of CRT in LC treatment was increasing progressively over the analysed period from 23.4% in 2009 to 40.6% in 2018. A quite comparable utility of treatment modalities in LC, additionally covering the earlier period is presented by Patel et al. in their analysis of the US National Cancer Database [18]. Their study involved 8,703 patients with stage III/IV LC treated between 2003 and 2011 and revealed the decline in total laryngectomies between 2003 and 2007 from 36.0% to 24.6%; in 2008, the utilisation of total laryngectomies increased to 27.8%, and remained within the range of 26.6% to 31.0% [18]. The use of open partial laryngectomies decreased from a peak incidence of 17.1% in 2003 and remained stable in the range of 9.0% to 10.4% up to 2011. The data presented show an evident rise in larynx-preserving CRT from 47% in 2003 to 61.5% in 2011 [18]. The review of Garcia Lorenzo et al. presents another similar comparison of treatment options offered to patients with T3 and T4 laryngeal cancer over the last 30 years, however from single institution in Spain [19]. They found out the surgery and RT were progressively substituted by CRT in chronological periods of 1985-1994, 1995-2004 and 2005-2014. The participation of surgery in treatment of LC patients declined from 62.5% to 52.2% and 50.5% respectively, while the percentages for RT were 33.5%, 39.7% and 16.8%, respectively. The contribution of CRT has risen from 0% to 8.1% and 32.7%, respectively. Moreover, the authors showed no significant differences in survival depending on treatment for T3 cancer patients, however, there was a significantly higher cancer-specific survival for T4 cancer patients treated surgically. The results of their report revealed the highest survival for patients from 1995 -2004 period and the lowest survival for those treated in the period of 2005–2014 [19]. The results of a recent meta-analysis by Tang et al. that include controlled trials and compare long-term survival, support total laryngectomy for patients with T4 LC and deny the advantage of primary organ preservation treatment for both T3 and T4 LC in increasing the overall survival rate [20]. Therefore, a treatment modality for advanced stages of LC should be addressed especially for further prospective studies. The other reason responsible for declining outcomes of LC that needs to be considered is the increasing age of patients at the primary diagnosis. With the shift of the average age, the presence of other comorbidities is also inevitable and may not only influence the survival but make some patients susceptible to specific therapy options.

Regarding the treatment modality for T1 stage of LC in retrospective reports, there is a relative equivalence of RT and transoral endoscopic microsurgery and the rates of local control exceed 90% [7]. However for T2 LC the rates decrease significantly and range between 70 and 80%, regardless of treatment approach [21]. Since the oncological benefits are comparable, both methods are verified in terms of voice and swallow outcomes, costs, side effects, time consumption, future options. The technological progress enabled the development of both methods in recent decades. The progress in visualization techniques and widespread adoption of laser techniques in laryngeal microsurgery

contribute to increased numbers of CO₂ laser endoscopic laryngeal resections of cancer, especially vocal cordectomies. We did not find the data directly analysing the increase in the utility of transoral procedures performed with the laser compared to cold instruments and open partial laryngectomies in glottic cancer. However, Mendelsohn et al. identified a substantial annual growth rates and correct growth rates in original studies covering glottic cancer and laryngeal cancer in the time following the European Laryngological Society classification of cordectomies in 2000 [22]. Unfortunately, the ICD-9 classification does not include specification of the 30.22 procedure regarding involvement of laser versus cold instruments. However according to worldwide trends, we assume that the increase of vocal cordectomies in Poland is inevitably correlated with widespread CO₂ laser endoscopic laryngeal microsurgery. The main advantages of laser-assisted LC treatment in comparison to RT are the short time of therapy, decreased costs, the possibility of revising endoscopic resection in case of persistence or recurrence and avoidance of the long-term side effects of RT.

In parallel to laser cordectomies, the new radiation techniques, including IMRT and stereotactic radiation therapy, are verified in studies dedicated to early stages of LC with analysis of sufficient doses (total dose and a single dose/fraction) and addition of sensitising CT [23].

There are limitations to our analysis, resulting mainly from the fact that the National Foundation Database is unfortunately not combined with the National Cancer Registry. Therefore the identification of LC stage with TNM was not possible due to access to ICD-10 diagnosis solely. Information concerning locoregional control, metastatic disease, prior or concurrent cancer diagnosis, received radiation doses, data regarding CT administration with a number of cycles, specific agents, doses and long-term toxicities is also missing.

Conclusions

The presented data revealed an increase in the total number of organ-preserving treatment modality with CRT in the subsequent years and a decreasing number of total laryngectomies in Polish patients with LC. The progressing age of LC onset in Polish population may contribute to declining outcomes. The multicenter prospective randomised studies comparing treatment modalities should be planned to verify the oncological outcomes and to refer them to patients' needs and cost-effectiveness.

Declarations:

Authors' contributions: Rzepakowska A. Conceptualization, methodology, writing, reviewing, editing and visualization. Żurek M: Methodology, data extraction, software and formal analysis, writing – draft, visualization. Niemczyk K. Reviewing, editing.

Conflicts of interest/Competing interests – none declared

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Data sharing statement: Deidentified individual participant data that underlie the results are reported in the article (text, tables, figures and supplementary file).

Ethics approval - All data used in the study were de-identified and therefore the approval of the Institutional Review Board was waived.

Patient consent for publication - Not required.

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Figure legends:

Figure 1. Different surgical procedures involving total laryngectomy, partial resection of the larynx or local destruction or excision applied to patients with laryngeal cancer in 2009-2018.

Figure 2. The proportional utilization of surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in treatment of laryngeal cancer in Poland in 2009-2018.

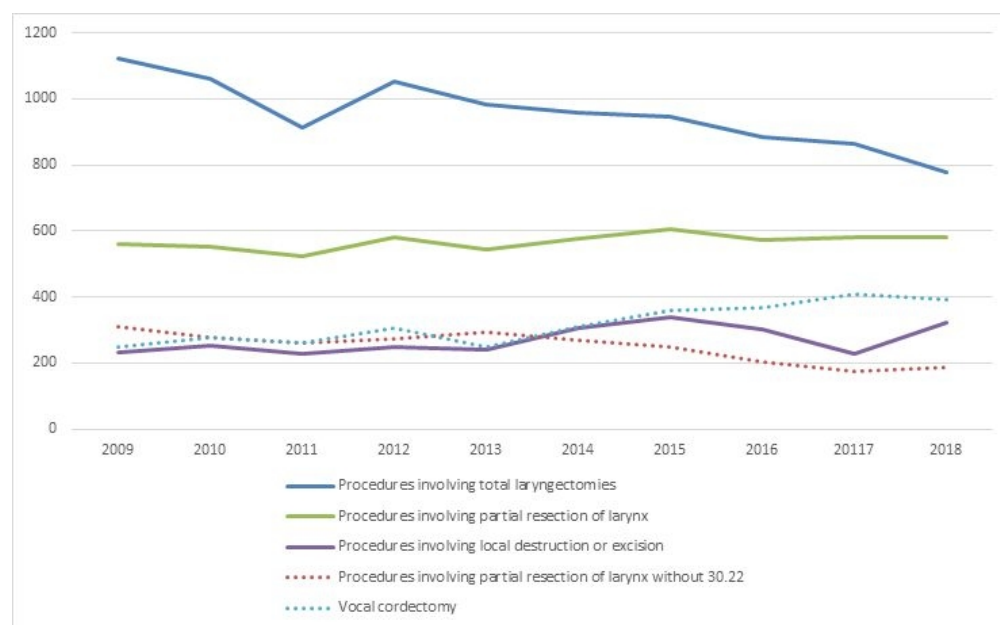


Figure 1. Different surgical procedures involving total laryngectomy, partial resection of the larynx or local destruction or excision applied to patients with laryngeal cancer in 2009-2018.

260x161mm (72 x 72 DPI)

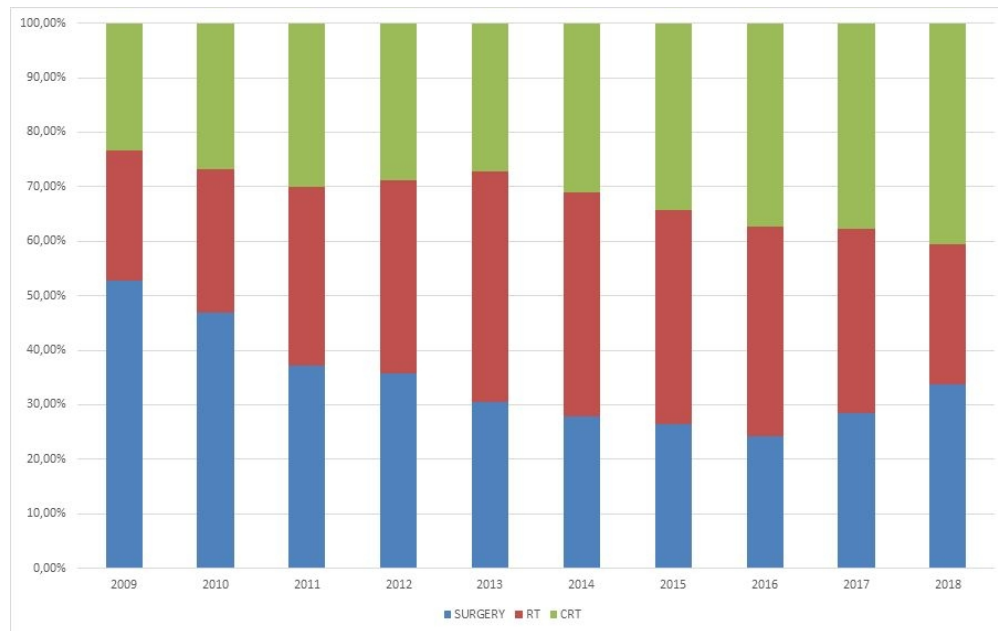


Figure 2. The proportional utilization of surgery, radiotherapy (RT) and chemoradiotherapy (CRT) in treatment of laryngeal cancer in Poland in 2009-2018.

319x201mm (72 x 72 DPI)

Table A. The number of surgical procedures according to ICD 9 codes applied to patients with laryngeal cancer during the 10 year period.

ICD9/Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Procedures involving total laryngectomies											
30.3 Complete laryngectomy	4	9	5	6	7	13	24	5	-	-	73
30.31 En bloc laryngeal resection with thyroidectomy and tracheostomy	85	70	39	79	48	33	27	20	15	14	430
30.32 Laryngopharyngectomy	521	472	470	517	539	527	559	547	551	531	5234
30.39 Other complete laryngectomy	347	351	245	303	241	221	202	203	188	153	2454
30.4 Radical laryngectomy (with radical neck dissection)	23	17	8	3	4	6	7	1	-	-	69
30.41 Radical laryngectomy (with radical neck dissection) and with thyroidectomy and tracheostomy	44	45	31	35	38	45	48	42	39	40	407
30.49 Other radical laryngectomy	98	96	115	109	108	113	81	67	70	38	895
Summary	1122	1060	913	1052	985	958	948	885	863	776	9562
Procedures involving partial resection of larynx											
30.1 Hemilaryngectomy	42	38	38	25	24	16	16	13	12	13	237
30.2 Other partial laryngectomy	-	3	2	-	-	1	-	-	-	-	6

30.21 Epiglottidectomy	15	11	7	10	10	6	10	5	1	6	81
30.22 Vocal cordectomy	250	276	262	307	249	309	358	369	409	393	3182
30.23 Partial laryngectomy with reconstruction	133	115	94	108	134	93	80	65	57	56	935
30.24 Laryngeal cartilage resection	1	1	1	1	1		3		2	2	12
30.29 Other partial laryngectomy	120	110	120	128	126	152	140	122	101	109	1228
Summary	561	554	524	579	544	577	607	574	582	579	5681
Procedures involving local destruction or excision of laryngeal tissue											
30.0 Excision or destruction of lesion or tissue of larynx	26	6	3	4	1	5	5	-	-	-	50
30.09 Other excision or destruction of lesion or tissue of larynx	161	167	165	176	151	165	210	167	123	186	1671
31.5 Local excision or destruction of larynx lesion or tissue of trachea	46	80	61	67	87	135	123	135	104	137	975
Summary	233	253	229	247	239	305	338	302	227	323	2696

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract Title page 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found Abstract page 2, results section
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Throughout the introduction, page 3
Objectives	3	State specific objectives, including any prespecified hypotheses The last paragraph of the introduction, page 3
Methods		
Study design	4	Present key elements of study design early in the paper The last paragraph of the methods section, page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Second paragraph of the methods section, page 4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Third paragraph of the methods section, page 4 (b) For matched studies, give matching criteria and number of exposed and unexposed - not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Third paragraph of the methods section, page 4
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - not applicable
Bias	9	Describe any efforts to address potential sources of bias - not applicable
Study size	10	Explain how the study size was arrived at Second paragraph of the methods section, page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Described in statistical analysis subsection, page 5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding Described in statistical analysis subsection, page 5 (b) Describe any methods used to examine subgroups and interactions Described in statistical analysis subsection, page 5 (c) Explain how missing data were addressed - not applicable (d) If applicable, explain how loss to follow-up was addressed - not applicable (e) Describe any sensitivity analyses - not applicable
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed The result section, page 5, table 1.

		(b) Give reasons for non-participation at each stage - not applicable
		(c) Consider use of a flow diagram - not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Throughout the result section, page 5 -8, table 1, table 2, table 3.
		(b) Indicate number of participants with missing data for each variable of interest - not applicable
		(c) Summarise follow-up time (eg, average and total amount) - not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time - not applicable
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included The results section, page 5, table 1
		(b) Report category boundaries when continuous variables were categorized - not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - not applicable
Discussion		
Key results	18	Summarise key results with reference to study objectives - page 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias The last paragraph of the discussion, page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Throughout the discussion page 9-11
Generalisability	21	Discuss the generalisability (external validity) of the study results - not applicable
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Declarations, page 11-12.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.