

# Proximal esophageal cancer

Citation for published version (APA):

de Vos-Geelen, J. (2021). *Proximal esophageal cancer*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20210625jv>

## Document status and date:

Published: 01/01/2021

## DOI:

[10.26481/dis.20210625jv](https://doi.org/10.26481/dis.20210625jv)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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## Summary

The proximal esophagus is the upper segment of the esophagus, consisting of the cervical part starting at the lower part of the cricoid cartilage to the thoracic inlet at approximately 18 cm from the incisors, and the upper thoracic part from the thoracic inlet to 24 cm from the incisors (**Chapter one**). Cancer of the proximal esophagus is an uncommon malignancy, with less than 5% of all esophageal cancers,<sup>1</sup> and poses several challenges to combat the current dismal prognosis. Incidence of proximal esophageal cancer in the Netherlands and optimal treatment modality of primary and recurrent disease was unknown. The main aim of this thesis was to investigate incidence and therapeutic patterns for patients with proximal esophageal cancer, in order to optimize patient treatment choices and subsequent outcomes in terms of quality of life and survival.

First, we assessed trends in stage distribution, treatment and its impact on outcome in patients with esophageal cancer in general (**Chapter two**) and proximal esophageal cancer specifically (**Chapter three**) diagnosed between 1989 and 2014 in the Netherlands. The aim was to gain more insight through real-life population cohorts, studying the developments in treatment strategies in order to optimize counseling of patients with (proximal) esophageal cancer. For these studies patients with (proximal) esophageal cancer were selected from the Netherlands Cancer Registry. Trends in stage distribution, treatment and survival rates were evaluated. Analyses were stratified by presence of distant metastasis.

In total, 35,760 patients with esophageal cancer were included (**Chapter two**). Age-standardized incidence rates increased from 5 per 100,000 inhabitants in 1989 to 9 in 2014, whereas mortality rates increased from 5 to 7 per 100,000 inhabitants. The incidence of esophageal adenocarcinoma increased, whereas the new cases with esophageal squamous cell cancer remained relatively stable. The proportion of cancers located in the cervical and upper thoracic part was <1-3% and 5-7%, respectively. Due to centralization, rates of resections performed in high-volume hospitals ( $\geq 20$  procedures per year) increased from 32% in 2005 to 92% in 2014. Neoadjuvant chemoradiation was performed more frequently in patients with non-metastatic esophageal adenocarcinoma and squamous cell cancer, respectively 4% and 2% in 2000-2004 to 43% and 26% in 2010-2014. The use of definitive chemoradiation increased as well, from 8% in 2000-2004 to 31% in 2010-2014 for non-metastatic esophageal squamous cell cancer, whereas this increase was less prominent for adenocarcinomas (3-14%). In metastatic disease, patients with adenocarcinomas received chemotherapy more frequently, and with squamous cell cancer underwent

more frequently radiotherapy and chemotherapy in more recent years. Five-year relative survival increased from 12% (standard error (SE): 0.9%) to 36% (SE: 0.9%) for non-metastatic adenocarcinoma and from 9% (SE: 0.7%) to 27% (SE: 1.2%) for non-metastatic squamous cell cancer over 26 years, particularly in the period 2005-2014. One-year relative survival for metastatic esophageal cancer increased from 15% (SE: 1.1%) to 22% (SE: 0.7%) between 1989 and 2014. We concluded that survival of patients with esophageal cancer improved significantly, which might be attributed to the centralization of surgery and the implementation of (neoadjuvant) chemoradiation.

In 1989-2014, 2,783 patients were diagnosed with proximal esophageal cancer in the Netherlands (**Chapter three**). In patients with non-metastatic proximal esophageal cancer (N=2,194), the use of surgery and radiotherapy was substituted by chemoradiation, the latter increasing from 1% in 1989-1994 to 49% in 2010-2014. Resection without neoadjuvant treatment was performed in 17% of patients in 1989-1994 and in 2% of patients in 2010-2014. The proportion of patients treated with neoadjuvant therapy and resection was relatively constant over time, varying between 3% and 7%. For patients with metastatic disease, only minor variations in treatment were observed, with a slight decrease in radiotherapy use and an increased appliance of chemotherapy and radiotherapy, concurrent or sequential, in 3% of patients in 1989-1994 and 23% of patients in 2010-2014. Chemotherapy alone was given to 7%-12% of patients in all time periods. Median overall survival of the total population increased from 7.3 months (95%CI: 6.4-8.1 months) in 1989-1994, to 9.5 months (95%CI: 8.1-10.8 months) in 2010-2014 (logrank  $P < 0.001$ ). In non-metastatic proximal esophageal cancer, five-year overall survival rates improved from 5% (95%CI: 3%-7%) in 1989-1994, to 13% (95%CI: 9%-17%) in 2010-2014 (logrank  $P < 0.001$ ). In patients with non-metastatic disease, time period effect disappeared after additional inclusion of treatment modality in the multivariable model. All treatment modalities had a statistically significant influence on overall survival compared with no localized treatment ( $P < 0.001$ ). Patients with non-metastatic proximal esophageal cancer treated with surgery with or without neoadjuvant therapy or treated with definitive chemoradiation showed 5-year overall survival rates of 31% (95%CI: 23%-40%), 21% (95%CI: 16%-28%), and 22% (95%CI: 19%-26%), respectively (logrank  $P = 0.32$ ). In patients with metastatic disease, overall survival did not change significantly over time (logrank  $P = 0.26$ ). This study showed that overall survival significantly improved in non-metastatic proximal esophageal cancer, likely to be associated with an increased use of definitive chemoradiation. Treatment patterns and outcome in metastatic disease did not change significantly over time.

In **Chapter four**, we present the results of a review of the literature on the diagnosis, treatment options and treatment-related complications of non-metastatic cervical esophageal cancer. Our review identified 107 publications describing a minimum of five patients diagnosed with cancer of the cervical esophagus and treated with curative intent.

We found that cervical esophageal cancer is rare, accounting for 2%-10% of all esophageal cancers. Tobacco and alcohol consumption seemed to be the major risk factors for developing cervical esophageal cancer. Patients with non-metastatic cervical esophageal cancer have a poor prognosis, with a 5-year overall survival of approximately 30%. These tumors are often locally advanced at presentation invading surrounding vital structures, e.g. upper respiratory tract, and are thus frequently unresectable at diagnosis. In other patients with resectable cervical esophageal cancer, surgery would implicate disabling resections including pharyngo-laryngo-esophagectomy, with accompanying decline in quality of life. Hence, curative strategies frequently include definitive chemoradiation, adapted by established regimens for lower esophageal or head and neck squamous cell cancer. However, definitive chemoradiation for cervical esophageal cancer is described to be accompanied by severe side-effects and complications. The urgency to progress in the management of cervical esophageal cancer warrants further research to explore which factors and treatment strategies are associated with improved outcomes.

This uncharted territory led to the initiation of a national comparative effectiveness study in proximal esophageal cancer, described in **Chapter five**. The objective of this study was to compare the treatment outcomes of four contemporary definitive chemoradiation regimens, based on cisplatin (Cis) or carboplatin plus paclitaxel (CP) combined with low ( $\leq 50.4$  Gy) or high ( $> 50.4$  Gy) dose radiotherapy (RT). We included 200 patients with locally advanced and unresectable squamous cell cancer of the proximal esophagus, from 11 centers in the Netherlands, treated with definitive chemoradiation between 2004-2014. Fifty-four, 39, 95, and 12 patients were treated with Cis-low-dose RT, Cis-high-dose RT, CP-low-dose RT, and CP-high-dose RT, respectively. Clinical complete response was achieved in 57% to 75% of patients, whereas the rate of complete response versus incomplete response was not significantly different between the four treatment groups ( $P=0.72$ ). Median overall survival was 21.9 months (95% CI: 16.9-27.0 months) and comparable between treatment groups (logrank  $P=0.88$ ), confirmed in the fully adjusted and propensity score weighted model ( $P>0.05$ ). Three-year overall survival rates were 35% (95% CI: 22%-48%) in the Cis-low-dose RT group compared with 46% (95% CI: 30%-61%), 40% (95% CI: 30%-50%), and 33% (95% CI: 10%-59%), in Cis-high-dose RT, CP-low-dose RT,

and CP-high-dose RT group, respectively. Multivariable analyses showed that the confidence intervals include 0.70, meaning that our study is not powered to state that there is no difference in survival between the four regimens. But, importantly, the point estimates of the hazard ratio approximate 1.0 for the different regimens, suggesting a possible overall survival difference would be small. Grades 3-5 acute adverse events were more frequent in patients treated with Cis-high-dose (OR 3.78;  $P=0.01$ ) or Cis-low-dose (OR 2.43;  $P=0.10$ ) versus CP-low-dose RT. The occurrence of grades 3-5 late toxicities was not different between the four treatment groups. This study could not establish a definitive conclusion regarding overall survival differences between the chemoradiation regimens. However, based on the superior safety profile, in addition to a more feasible outpatient implementation, we suggest a chemoradiation regimen with carboplatin and paclitaxel to be standard in the curative setting for patients with locally advanced proximal esophageal cancer.

The national comparative effectiveness study in unresectable proximal esophageal squamous cell cancer was furthermore used to determine the patterns of recurrence and overall survival in patients achieving clinical complete response after treatment with definitive chemoradiation (**Chapter six**). In 197 of the 200 identified patients, response was evaluated, among which 133 (68%) showed a complete response. In complete responders, median overall survival, 3-year overall survival, and progression-free survival were 45.0 months, 58%, and 49%, respectively. Three- and 5-year risk of recurrence were 40% and 45%. Three- and 5-year risk of locoregional recurrence were 26% and 30%. Eight of 32 patients with an isolated locoregional recurrence underwent salvage surgery, with a median overall survival of 32.0 months (95% CI 6.8-not reached). We concluded that most recurrences after complete response following definitive chemoradiation for unresectable proximal esophageal cancer were locoregional and developed within the first three years after chemoradiation. These findings suggest to enhance and restrict locoregional follow-up during the first three years following chemoradiation.

## Reference

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## Samenvatting

In Nederland worden per jaar ongeveer 2500 patiënten met slokdarmkanker gediagnosticeerd. Kanker van het bovenste deel van de slokdarm komt in 1 op de 20 patiënten met slokdarmkanker voor en is derhalve een zeldzame aandoening. Slokdarmkanker kan met veel symptomen gepaard gaan, waaronder moeite of pijn bij het slikken en gewichtsverlies. De hoeksteen van de behandeling van kanker in zijn algemeenheid is chirurgische verwijdering. Bij slokdarmkanker is een operatie echter geen sinecure en kan gepaard gaan met ernstige complicaties. Kanker van het bovenste deel van de slokdarm ligt zeer ongunstig voor een operatieve ingreep door de nabijheid van vele cruciale structuren die noodzakelijk zijn voor een kwalitatief goed bestaan. Met name de overgang van de mondholte naar de stembanden en luchtpijp grenzen aan het bovenste deel van de slokdarm. Een operatie zou derhalve resulteren in een mutilerende situatie waarbij het vermogen tot spreken en slikken onnatuurlijk zal zijn. Daarom is het essentieel om te bestuderen welke behandelopties er zijn voor deze patiënten. Op deze manier kan elke patiënt zo goed mogelijk worden geïnformeerd over de mogelijke behandelopties, risico's op complicaties en verwachte effecten, alvorens tot besluitvorming door een patiënt en de behandelend arts wordt overgegaan.

Dit proefschrift toont dat het aantal patiënten dat in Nederland werd gediagnosticeerd met slokdarmkanker toenam over de tijd, van 5 per 100.000 inwoners per jaar in 1989-1994 naar 9 per 100.000 inwoners per jaar in 2010-2014. De kans om aan de ziekte te overlijden nam af, waarbij in 1989-1994 maar 1 op de 13 patiënten 5 jaar na de diagnose in leven was, is dit in 2010-2014 gestegen naar 1 op de 4 patiënten. Deze winst is met name te verklaren door de toepassing van een gecombineerde behandeling van chemotherapie en radiotherapie ('chemoradiatie'), zowel vooraf aan een eventuele operatie ('neoadjuvante setting') als bij patiënten die geen operatie kunnen ondergaan ten gevolge van te uitgebreide lokale groei of doordat ze niet fit genoeg worden geacht voor een operatieve ingreep ('definitieve setting'). Daarnaast worden slokdarm operaties vanaf 2006 verricht in een expertisecentrum voor slokdarmkanker om de hoog specialistische chirurgische zorg te bundelen, waarbij in eerdere studies werd gezien dat deze centralisatie bijdraagt aan een betere uitkomst voor de patiënt.

Ook bij patiënten met kanker in het bovenste deel van de slokdarm zagen we een soortgelijke trend in overleving. We zagen dat de chemoradiatie zijn intrede deed, waarbij in 1989-1994 nog maar 1% van de patiënten met lokale ziekte werd behandeld

met definitieve chemoradiatie, nam dit toe tot 49% in 2010-2014. Gelijktijdig nam de toepassing van operaties en radiotherapie zonder chemotherapie af. Ondanks dat wellicht fittere patiënten een operatie ondergingen, zagen we dat de overleving min of meer gelijk was tussen patiënten die werden behandeld met een operatie, met of zonder neoadjuvante therapie, of met definitieve chemoradiatie, waarbij 1 op de 4 patiënten 5 jaar na de diagnose nog in leven was. Omdat chemoradiatie tot minder ernstige complicaties leidt dan een operatie, is het toepassen van chemoradiatie zonder een operatie op dit moment de beste behandelmodaliteit. Bij patiënten met uitgezaaide kanker vanuit het bovenste deel van de slokdarm werd over de tijd iets meer chemotherapie toegepast, hoewel de overleving hier niet evident door verbeterde.

Chemoradiatie kan uit verschillende soorten (combinaties van) chemotherapie en uiteenlopende doses radiotherapie bestaan. We hebben onderzocht welke combinatie de beste uitkomsten gaf voor patiënten met kanker van het bovenste deel van de slokdarm. Hiervoor vergeleken we 4 behandelgroepen bestaande uit cisplatin chemotherapie met lage dosis radiotherapie ( $\leq 50$  Gy), cisplatin chemotherapie met hoge dosis radiotherapie ( $> 50$  Gy), carboplatin plus paclitaxel chemotherapie en lage dosis radiotherapie of carboplatin plus paclitaxel chemotherapie en hoge dosis radiotherapie. Deze studie toont dat de overleving van patiënten uit alle 4 behandelgroepen vergelijkbaar was. Wel zagen we dat ernstige bijwerkingen duidelijk minder vaak voorkwamen bij 1 van de 4 groepen, namelijk patiënten die werden behandeld met carboplatin plus paclitaxel chemotherapie en lage dosis radiotherapie. Aangezien de kwaliteit van leven enorm beïnvloed kan worden door deze (ernstige) bijwerkingen ligt de voorkeur voor het chemoradiatie schema met de laagste kans op bijwerkingen voor de hand. Tevens wordt deze behandeling (carboplatin-paclitaxel) op de dagverpleging toegediend, in tegenstelling tot (een deel van de) cisplatin behandelingen, waarbij patiënten worden opgenomen en gedurende een etmaal een infuus krijgen ten behoeve van toediening van de chemotherapie.

Bij 133 van de 200 patiënten zagen we dat de kanker van het bovenste deel van de slokdarm volledig leek te verdwijnen door de definitieve chemoradiatie. Deze patiënten hadden een evident betere prognose dan patiënten waarbij nog rest tumor aanwezig was na chemoradiatie. We hebben in dit proefschrift gekeken naar patronen van terugkeer van ziekte bij de groep patiënten waarbij de ziekte volledig verdwenen leek na de chemoradiatie. Ondanks de initieel goede respons op de chemoradiatie, zagen we bij 44% alsnog terugkeer van ziekte. Het meest frequent keerde de kanker terug in het gebied van de oorspronkelijke tumor, dus in het bestraalde gebied. Behandeling



van teruggekeerde kanker in dit gebied dient op individueel niveau te worden beoordeeld door patiënt en behandelend arts, waarbij kan worden besloten tot bestraling, chemotherapie, geen anti-tumor behandeling of, in uitzonderlijke gevallen, een operatie. Deze studie toont dat als de kanker terugkeert, dit voornamelijk in de eerste 3 jaar na de behandeling is. Dit heeft tot het voorstel geleid om bij de opvolging na chemoradiatie de aandacht op terugkeer van ziekte in het bestraalde gebied te verbeteren, waarbij er kan worden overwogen om na 3 jaar geen standaard opvolging meer te verrichten, tenzij dit op basis van andere factoren, bijvoorbeeld slokdarmoprekkingen, diëtetiek of psychosociale begeleiding, noodzakelijk wordt geacht.