**Outcomes and survival following neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the esophagus: inverse propensity score weighted analysis**

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**Abstract**

**Background:** Esophageal cancer is increasingly common and carries a poor prognosis. The optimal treatment modality for locally advanced cancer is unknown, with current guidance recommending either neoadjuvant chemotherapy (CT) or chemoradiotherapy (CRT) followed by surgery. There is a lack of adequately powered trials comparing CT against CRT. We retrospectively compared CT versus CRT using a propensity score weighting approach.

**Methods:** Demographic, disease, treatment and outcome data were retrieved from a local database for patients who received neoadjuvant CT or CRT followed by surgery. Inverse probability of treatment weighting (IPTW) was used to balance groups using a propensity score-weighting approach. Groups were assessed for differences in postoperative outcomes and survival. Kaplan-Meier and non-parametric tests were used to compare survival and outcome data as appropriate.

**Results:** Data for 284 patients were retrieved. Following IPTW groups were well matched. No significant differences were seen for postoperative complications (CT 64.9% vs. CRT 63.3%, p=0.807), including major complications (24.0% vs. 23.6%, p=0.943) and anastomotic leak (7.8% vs. 5.6%, p=0.526). Significantly higher rates of clinical regression and complete pathological response were seen following CRT (p=0.002 for both). Rates of R0 resection were higher with CRT, CT 79.1% vs. CRT 93.1%, p=0.006. There was no difference between groups for overall or disease-free survival.

**Conclusion:** This study suggests that the significant improvements in local tumour response seen after neoadjuvant CRT compared to CT may not translate to different survival outcomes. However, it must be stressed that adequately powered prospective trials are still lacking.

**Introduction**

Esophageal cancer is among the most common cancers worldwide. Incidence in Western countries is increasing, with a predominance of adenocarcinoma, whereas incidence of squamous cell carcinoma (SCC) is in decline.1 Despite continued improvements in surgical and oncological treatment, prognosis for esophageal cancer remains poor.

The optimal treatment modality for locally advanced cancer is unknown. Current treatment recommendations from major international societies including the European Society of Medical Oncology (ESMO)2, National Comprehensive Cancer Network (NCCN)3, and British Society for Gastroenterology (BSG)4 are unanimous in recommending multimodal treatment but are not prescriptive for the regimen to be given. With the exception of very early stage tumours, all recommend either perioperative chemotherapy (CT) or neoadjuvant chemoradiotherapy (CRT). This has resulted in variable practice and treatment regimens.5

Such variance highlights the fact that current opinion on the best method of perioperative treatment is divided. Major trials that have influenced the perioperative treatment of gastroesophageal cancer over the last 20 years have compared neoadjuvant treatment in the form of CT6, 7 plus surgery or CRT8 plus surgery, to surgery alone. Two trials have compared chemotherapy regimens. The British OE05 trial9 demonstrated no benefit from a more intensive 4 cycle CT protocol of epirubicin, cisplatin and fluorouracil (ECF) over cisplatin and fluorouracil (CF). More recently the German FLOT4 trial10 has shown improved overall with perioperative fluorouracil, leucovorin, oxaliplatin and docetaxel. These trials have further all suffered from varying degrees of heterogeneity by including gastric and oesophageal cancers in variable proportions, as well as both adenocarcinoma and squamous cell cancers.

There have been few trials comparing CRT against CT. The German POET trial11 aimed to compare CT vs CRT, but was closed early due to lack of patient accrual. Other studies were also limited to small sample sizes12, 13. On-going randomised studies such as the TOPGEAR14 (which has reported interim feasibility but not survival data), European ESOPEC15 or UK-based Neo-AEGIS16 trials aim to provide better evidence to support one modality over the other; formal reporting of these trials is awaited.

We wished to compare our centre’s outcomes for neoadjuvant CT versus CRT. Even in high volume centres, case volumes may be insufficient to allow meaningful conclusions from a multivariate analysis to be drawn. We utilised a propensity score weighting approach, inverse probability of treatment weighting (IPTW), to appropriately match patient preoperative characteristics for the likelihood of receiving either neoadjuvant CT or CRT, to assess the effects of each on clinical, histopathological, and survival outcomes.

**Methods**

*Patient Selection*

Following institutional approval, data for all sequential patients from Jan 2010 – August 2019 inclusive who received neoadjuvant CT or CRT followed by surgery were retrieved from a prospectively maintained electronic database. Prior to 2013, patients at our centre received exclusively CT. Following publication of the CROSS study, CRT was increasingly introduced into practice, with 54% of patients from 2013-2019 receiving CRT. Once established, the proportion of patients receiving CRT was fairly static without appreciable temporal trend, from 2015-2019 an annualised median of 64.5% patients received CRT. Selection of neoadjuvant therapy was decided upon in consultation with the multidisciplinary team (tumour board). Demographic, disease, treatment, and outcome data were recorded. Complications of surgery were defined according to the ECCG criteria.17

*Outcome Measures*

The primary outcome measures were overall survival (OS) and disease-free survival (DFS). Secondary outcome measures included surgical complications, post-operative pathology, and early recurrence.

*Missing Data*

Missing data was handled using multiple imputation by chained equations (MICE)18 with 5 imputed datasets. Both primary and secondary outcome measures were not imputed, and missing data in the outcome field was handled by listwise deletion.

*Inverse Probability of Treatment Weighting (IPTW)*

To reduce the influence of confounding factors in this retrospective, non-randomised study, a propensity score weighting approach was taken. The propensity score is defined as the probability of receiving a treatment (in this case chemotherapy or chemoradiotherapy) conditional on specified covariates.19 It is equivalent to the probability yielded from a logistic regression model where the treatment is considered as a binary dependent variable and the specified list of covariates to balance considered as the independent variables. Each case was then weighted according to the inverse propensity score for the treatment that was received. This process creates a weighted cohort of patients that is well balanced and appropriate for direct comparison. As each case is weighted individually the apparent number of cases in each treatment group may be non-integer. IPTW has been shown to be an effective means of balancing covariates across treatment classes,20 and often has superior performance to propensity score matching, particularly with low sample size,21 as it allows all cases to be considered in the final analysis.

As our data contained missing values, the final IPTW was calculated as an average of that generated in each imputed dataset as has been described previously.22 Covariates included in the propensity score calculation were gender, age, ASA, cT stage, cN stage, tumour type, tumour location.

*Assessment of covariate balance*

Balance before and after IPTW was assessed using the standardised mean difference (SMD) between groups. A SMD of greater than 0.1 is usually considered to indicate a significant imbalance.23

*Statistical Analysis*

Hypothesis testing was conducted using the Mann Whitney U test and the Chi-Square test for non-parametric data, weighted in the IPTW sample. Survival analysis was conducted using the Kaplan Meier estimator and the Log-rank test, again weighted in the IPTW sample. p <0.05 was considered statistically significant. While the overall analysis controlled for tumour type as part of IPTW, we also considered adenocarcinoma and squamous cell carcinoma subgroups separately. All analysis was conducted in R 3.5.3.

**Results**

Data for 284 patients who underwent neoadjuvant CT or CRT followed by esophagectomy with two-field lymphadenectomy with curative intent were included. 100% of CRT was given according to CROSS regimen. CT patients received epirubicin, oxaliplatin, and capcitabine (EOX, 53.6%), epirubicin, cisplatin, and fluoruracil/capcitabine (ECF/ECX, 32.6%), capcitabine and oxaliplatin (CAPOX, 6.5%), or fluoruracil, leucovorin, oxaliplatin, and docetaxel (FLOT, 7.2%). Tumour types included 79.2% (n=225/284) of patients with adenocarcinoma, 20.8% (n=59/284) had SCC. Tumour location was predominantly of the distal esophagus or gastro-esophageal junction. Patients receiving CT or CRT were similar for age, ASA, radiological T and N stages; CRT patients were more likely to be female, had a greater proportion of non-junctional tumours, and SCC (table 1).

IPTW performed well at balancing the selected covariates across the cohort, as evidenced by the improvement in SMD (see figure 1). Prior to IPTW 6 of 7 variables had a SMD of greater than 0.1. Following propensity score-matched adjustment for gender, age, ASA grade, cT stage, cN stage, tumour type (SCC vs adenocarcinoma), and location (GOJ, distal, or proximal esophagus) these differences were eliminated (see table 2).

Overall postoperative follow-up was median 40 months (IQR 20 – 60 months); 58 (34-63) months for the CT group and 26 (14-38) months for the CRT group. Following IPTW adjustment, overall complication rates, major complication rates and rates of anastomotic leak (7.8% vs. 5.6%, p=0.526) were similar between groups (see appendix 1). Postoperatively, rates of major complications (Clavien-Dindo grade 3 or greater, CT 24.0% vs. CRT 23.6%, p=0.943), overall complications (64.9% vs. 63.3%, p=0.807), anastomotic leak (7.8% vs. 5.6%, p=0.526), and unplanned returns to theatre or higher dependency settings were also equal between groups. While in the CT group, the rate of chyle leak was lower (3.6% vs. 11.6%, p=0.017), the median length of stay was higher (11 days vs. 9 days, p=0.007).

There were significant differences in the histopathological response to treatment. Significantly higher rates of clinical regression (T stage) were seen following CRT (p=0.002), with complete pathological response seen in 7.5% of CT patients, compared to 20.9% for CRT (p=0.002). Accordingly better rates of TRG-response (p<0.001), and R0 resection (CT 79.1% vs. CRT 93.1%, p=0.006) were seen.

Prior to IPTW, CRT demonstrated superior OS; however, this survival advantage was not statistically significant after IPTW adjustment (see figure 2). There was no statistically significant difference for DFS (see figure 3) or early recurrence (less than 12 months) between groups (unadjusted CT 27.6% vs. CRT 25.9%, p = 0.954; IPTW 27.1% vs. 30.8%, p = 0.879). OS and DFS in patients with SCC was higher with NACRT compared to NACT (Figures 2 and 3, OS p = 0.026, DFS p = 0.004)

Analysing patients with adenocarcinoma separately similar trends were observed (table 3). Within this group, postoperative pathology remained more favourable after CRT, with better rates of TRG-response (p<0.001) and R0 resection (CT 80.0% vs CRT 94.3%, p=0.014). Increased T-stage regression and complete pathological response with CRT were however no longer statistically significant (p=0.071 and p=0.131 respectively). Survival outcomes were also equivalent.

In patients with SCC (table 4), the pathological complete response rate was superior with NACRT (46.1% vs 7.2%, p = 0.005). Median survival was also superior; 23 months with NACT versus median not reached with NACRT (p<0.001).

**Discussion**

This study suggests that the significant improvements in local tumour response seen after neoadjuvant CRT compared to CT may not translate to different longer-term outcomes in oesophageal adenocarcinoma. Despite significantly higher rates of pathological complete response, TRG 1/2, and R0 resection after neoadjuvant CRT, no differences in overall and disease-free survival were seen following IPTW case-matching to adjust for patient demographics, tumour location, type, and stage. This was not the case in SCC, where survival in our cohort was superior following CRT compared to CT, reflecting the known differences between adenocarcinoma and SCC disease types and their susceptibility to radiotherapy.

The lack of adequately powered randomised trials has meant that a lack of clarity on the best choice of neoadjuvant treatment for esophageal cancer remains. We utilised IPTW weighting, which has been shown to produce a lower standardised mean difference in covariates (and hence better balance) in comparison to standard propensity score-matching,21 in an effort to control for factors in this retrospective single centre sample. The result is one of the largest retrospective datasets of its kind, allowing for case-matched comparisons between groups.

The clinicopathological data presented in this study is comparable to other published literature on the topic. Deng et al24 performed a meta-analysis of randomised trials, and reported an R0 rate of 76.9% after CT and 89.1% CRT (compared to 79.1% and 93.1%, respectively, in our study). Other standard propensity score-matched cohorts have reported very similar results.25, 26

The lack of a statistically significant difference in OS and DFS is in agreement with other studies. Visser et al25 (n=131 in each group) and Markar et al26 (n=221 in each group) reported standard propensity score-matched cohorts, and reported no difference between survival rates. Petrelli et al27 performed a meta-analysis of trials, including retrospective cohort studies, for adenocarcinoma and reported no difference in OS (p=0.41).

The significance of neoadjuvant therapy selection and response is manifold. Two European trials, ESOSTRATE28 and SANO,29 are testing the hypothesis that patients with a clinical complete response after neoadjuvant therapy do not require esophagectomy. Patients will be randomised to surgery or a watchful waiting approach. Proponents of a watchful waiting approach argue that recurrences may be predominantly due to disease outside the local radiotherapy field, and which would not be resected as part of a surgical specimen. There is, however no evidence to support this hypothesis and where persistent cells are found following CRT it is frequently at depth (62% in the serosa) and within the radiation field.30 It may be more likely that the desmoplastic reaction seen in the tumour bed of responders after CRT does not represent elimination of the cancer cells but rather the cancer cells persist beneath the threshold for detection by current histopathological techniques. These remaining cells are likely to be resistant to further CRT and more prone to metastasis.31 All of the evidence for a survival benefit after pathological complete response (pCR) comes from patients who have gone on to have an esophagectomy and we would urge caution.

Definitive radiotherapy is acknowledged to be a viable treatment option for SCC of the oesophagus. However, not only is the histological type more susceptible8 but there is increasing evidence that the two histological subtypes have a different natural history along with their different cell of origin and should be treated as oncologically separate diseases.32

Regardless of perioperative therapy it is clear that responders derive a significant survival benefit while non-responders, who still make up the majority, do not.33 The community is lacking a means to identify *ab initio* which patients will benefit. A number of molecular and radiological biomarkers are in development including the use of PET CT34 and next generation genetic sequencing and predictive technologies.35, 36

It has also been suggested that the selection of neoadjuvant therapy may have an implication for postoperative complications. Different chemotherapy regimens will have different side-effect profiles and complication rates. Radiotherapy may impair healing, particularly if any part of the gastric conduit or relevant arterial supply is exposed to the radiotherapy field. Major complications have been shown to potentially impact negatively on disease recurrence and survival.37, 38 In a meta-analysis of four clinical trials, while three of the four included studies did not report a statistically significant difference, Fan et al39 found that after pooling of data, a higher rate of complications occurred in the CRT group. However, this data was heterogenous (I2 = 86.8%) and skewed by the only study to find a significant difference between groups, which included patients from multiple clinical trials dating back almost 30 years. Markar et al reported a significantly higher rate of anastomotic leak after CRT in their multi-centre retrospective study, but speculated this may have been confounded by difference in surgical approaches between groups.26 In the present study, we found an increased incidence of chyle leak in the CRT group. However, this did not appear to have any effect on overall length of stay, which was shorter than the CT group. The clinical relevance of this is unclear, and there were no statistical differences in rates of pulmonary complications, anastomotic leak, or overall complication rates in our group.

This study represents one of the largest cohort of patients assessed in a retrospective, propensity score-weighted fashion. Data was recorded from patients over a relatively short timeframe (nine years) from a single high-volume tertiary centre, thereby limiting confounding from different surgeons, and techniques. We were unable to control for other factors such as the regimen or dose of neoadjuvant therapy received, which while partially controlled for through matching of disease stages, is subject to selection bias through treatment decisions of the multi-disciplinary team and temporal shifts in neoadjuvant therapy as described, or nodal harvest. An additional sensitivity analysis controlling for operative approach (more than half of patients underwent a laparoscopic abdominal and thoracoscopic chest approach) did not have any impact on outcome. While our study assessed a sample which included 20.8% of patients who had SCC, this was controlled for as part of the IPTW propensity score matching. Additionally, a subgroup analysis in patients with adenocarcinoma only revealed similar results, with a smaller margin of effect, in line with the known enhanced radiosensitivity of oesophageal SCC compared to adenocarcinoma.8 We have not differentiated between Siewert classification tumour types in our analysis, as this data was incomplete in our dataset. Subgroup analysis for the available data did not demonstrate any meaningful change in outcome between groups; our centre’s practice has been to treat high and “true” junctional (i.e. Siewert I and II) tumours with esophagectomy, as is also current TNM8 guidance. Our institution also started an enhanced recovery programme in 2013,40 with increasingly successful implementation and compliance throughout the period of data presented here. We believe this accounts for the shorter length of stay seen after nCRT, as a higher proportion of these patients were cared for with an enhanced recovery programme established. A further sub-analysis comparing data from 2013 onward only demonstrated no significant difference in length of stay (p = 0.959) between CRT and CT groups, with no significant differences in other outcomes to the overall analysis.

The results of this study would appear to suggest that in the context of currently available evidence, patient selection and response to neoadjuvant therapy may be more important than the choice of neoadjuvant therapy alone. Our report agrees with other published data, which suggest that the improvement of R0 rates and downstaging of disease following CRT do not result in corresponding gains in long-term survival. The cause for this discrepancy is unclear. Visser et al, considering the patterns of recurrence in their cohort of 191 patients, found no difference in recurrence rates or location of recurrence (local recurrence, regional or distant metastases).25 In this context it is an important concept that pathological outcomes appear to be an inadequate surrogate for patient level survival outcomes, particularly when comparing treatments. This should be considered when designing future trials and also in the next iteration of TNM staging.

However, it must be stressed that adequately powered studies are lacking, with further prospective trials are ongoing. Retrospective trials such as this study are subject to bias, particularly given that they often involve heterogenous chemotherapy regimens which may no longer be the standard of care. The emergence of taxane therapy in FLOT-type regimens has the potential to supersede older MAGIC-type chemotherapy, but its efficacy compared to chemoradiotherapy is unclear. Ongoing trials such as NeoAEGIS seek to answer this question and provide clarity in future, however may lack the power to demonstrate subtle differences in survival. Current practice should continue to weigh treatment options on a case by case basis, with informed decision-making shared between surgeon, oncologist, and patient.

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**Figure 1: Covariate Balance before and after IPTW**

![A close up of a map

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**Figure 2: Overall Survival in all patients and by histological subtype**

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**Figure 3: Disease Free Survival in all patients and by histological subtype**

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**Table 1. Clinicopathological Characteristics before IPTW**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Unadjusted Demographics** | | | | |
|  |  | **Chemotherapy** (n = 166) | **Chemoradiotherapy** (n = 118) | p§ |
| **Male** |  | 139 (83.7) | 81 (68.6) | **0.004\*** |
| **Age** |  | 65.03 [58.20, 69.56] | 65.96 [59.56, 71.93] | 0.323¶ |
| **ASA** |  |  |  | 0.429 |
|  | **1** | 11 ( 6.6) | 9 ( 7.6) |  |
|  | **2** | 104 (62.7) | 81 (68.6) |  |
|  | **3** | 51 (30.7) | 28 (23.7) |  |
| **cT Stage** |  |  |  | 0.851 |
|  | **0** | 1 ( 0.6) | 0 ( 0.0) |  |
|  | **1** | 0 (0.0) | 0 (0.0) |  |
|  | **2** | 30 (18.1) | 20 (16.9) |  |
|  | **3** | 118 (71.1) | 86 (72.9) |  |
|  | **4** | 17 (10.2) | 12 (10.2) |  |
| **cN Stage** |  |  |  | 0.802 |
|  | **0** | 35 (21.1) | 21 (17.9) |  |
|  | **1** | 114 (68.7) | 83 (70.9) |  |
|  | **2** | 17 (10.2) | 13 (11.1) |  |
| **SCC** |  | 14 ( 8.4) | 45 (38.1) | **<0.001\*** |
| **Tumour Location** | |  |  | **<0.001\*** |
|  | **GOJ** | 74 (44.6) | 19 (16.2) |  |
|  | **Distal Oesophagus** | 92 (55.4) | 97 (82.9) |  |
|  | **Proximal Oesophagus** | 0 ( 0.0) | 1 ( 0.9) |  |
| Data presented as absolute number (%) and median (IQR), \*<0.05, | | | | |
| § χ2 test, except ¶ Mann–Whitney U test | | | | |

**Table 2. Clinicopathological Characteristics after IPTW**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Weighted Sample Demographics** | | | | |
|  |  | **Chemotherapy (n = 166.0)** | **Chemoradiotherapy (n = 117.5)** | **p§** |
| **Male** |  | 130.5 (78.6) | 92.5 (78.7) | 0.986 |
| **Age** |  | 65.60 [58.27, 70.57] | 65.01 [59.18, 71.32] | 0.959¶ |
| **ASA** |  |  |  | 0.997 |
|  | **1** | 9.3 ( 5.6) | 6.5 ( 5.5) |  |
|  | **2** | 111.5 (67.2) | 179.4 (67.6) |  |
|  | **3** | 45.2 (27.2) | 31.5 (26.8) |  |
| **cT Stage** |  |  |  | 0.913 |
|  | **0** | 0.6 ( 0.4) | 0.0 ( 0.0) |  |
|  | **1** | 0 (0.0) | 0.0 (0.0) |  |
|  | **2** | 26.8 (16.2) | 18.1 (15.4) |  |
|  | **3** | 124.5 (75.0) | 88.9 (75.7) |  |
|  | **4** | 14.2 ( 8.5) | 10.4 ( 8.9) |  |
| **cN Stage** |  |  |  | 0.825 |
|  | **0** | 33.2 (20.0) | 25.0 (21.4) |  |
|  | **1** | 115.9 (69.8) | 77.3 (66.2) |  |
|  | **2** | 16.9 (10.2) | 14.5 (12.4) |  |
| **SCC** |  | 35.0 (21.1) | 24.2 (20.6) | 0.930 |
| **Tumour Location** | |  |  | 0.663 |
|  | **GOJ** | 54.5 (32.8) | 39.0 (33.5) |  |
|  | **Distal Oesophagus** | 111.5 (67.2) | 77.0 (66.2) |  |
|  | **Proximal Oesophagus** | 0.0 ( 0.0) | 0.4 ( 0.4) |  |
| Data presented as absolute number (%) and median (IQR), \*<0.05, | | | | |
| § χ2 test, except ¶ Mann–Whitney U test | | | | |

**Table 3. Clinical and Pathological Outcomes before and after IPTW (adenocarcinoma only)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Unadjusted Outcomes | | | Weighted Sample Outcomes | | |
|  |  | CT (n = 152) | CRT (n = 73) | p§ | CT (n = 131.0) | CRT (n = 93.3) | p§ |
| Complications | | 98 (64.5) | 45 (61.6) | 0.791 | 85.1 (64.9) | 57.7 (61.8) | 0.706 |
| Anastomotic Leak | | 8 ( 5.3) | 4 ( 5.5) | 1.000 | 6.9 ( 5.3) | 4.3 ( 4.6) | 0.834 |
| Pulmonary Complications | | 59 (38.8) | 23 (31.5) | 0.358 | 51.1 (39.0) | 30.8 (33.0) | 0.475 |
| Chyle Leak | | 7 ( 4.6) | 6 ( 8.2) | 0.434 | 6.0 ( 4.6) | 10.6 (11.3) | 0.118 |
| Length of Stay | | 10 [8, 14] | 9 [8, 11] | 0.05 | 10 (8, 14) | 9 (8, 11) | 0.070¶ |
| Return to Theatre | | 14 ( 9.2) | 5 ( 6.8) | 0.734 | 11.0 ( 8.5) | 7.8 (8.4) | 0.948 |
| Unplanned Escalation of Care | | 20 (13.2) | 13 (17.8) | 0.470 | 16.8 (12.8) | 17.5 (18.8) | 0.217 |
| Major Complication (CD3a-5) | | 36 (23.7) | 16 (21.9) | 0.900 | 29.8 (22.8) | 21.2 (22.8) | 0.952 |
| In Hospital Mortality | | 0 ( 0.0) | 1 ( 1.4) | 0.707 | 0.0 ( 0.0) | 1.0 (1.1) | 0.309 |
| ypT Stage | 0 | 12 ( 7.9) | 16 (21.9) | **0.030\*** | 11.0 ( 8.4) | 18.3 (21.3) | 0.071 |
|  | 1 | 39 (25.7) | 16 (21.9) |  | 32.7 (25.0) | 17.7 (18.9) |  |
|  | 2 | 23 (15.1) | 13 (17.8) |  | 21.2 (16.1) | 17.6 (18.9) |  |
|  | 3 | 76 (50.0) | 28 (38.4) |  | 64.5 (49.3) | 38.1 (40.8) |  |
|  | 4 | 2 ( 1.3) | 0 ( 0.0) |  | 1.5 ( 1.2) | 0.0 ( 0.0) |  |
| ypN Stage | 0 | 78 (51.3) | 35 (47.9) | **0.041\*** | 68.5 (52.2) | 46.1 (49.4) | **0.029\*** |
|  | 1 | 28 (18.4) | 22 (30.1) |  | 24.0 (18.3) | 24.9 (26.7) |  |
|  | 2 | 27 (17.8) | 14 (19.2) |  | 22.0 (16.8) | 20.3 (21.8) |  |
|  | 3 | 19 (12.5) | 2 ( 2.7) |  | 16.5 (12.6) | 2.0 (2.2) |  |
| Response to Neoadjuvant Therapy | TRG 1 | 16 (10.6) | 14 (19.2) | **<0.001\*** | 14.3 (11.0) | 17.8 (19.1) | **<0.001\*** |
|  | TRG 2 | 27 (17.9) | 24 (32.9) |  | 23.3 (18.0) | 31.9 (34.1) |  |
|  | TRG 3 | 20 (13.2) | 17 (23.3) |  | 16.7 (12.9) | 21.6 (23.2) |  |
|  | TRG 4 | 42 (27.8) | 15 (20.5) |  | 36.7 (28.2) | 18.7 (20.1) |  |
|  | TRG 5 | 42 (27.8) | 3 ( 4.1) |  | 35.8 (27.5) | 3.3 (3.5) |  |
|  | Unknown | 4 ( 2.6) | 0 ( 0.0) |  | 3.1 ( 2.4) | 0.0 ( 0.0) |  |
| Vascular Invasion | | 47 (30.9) | 14 (19.2) | 0.090 | 40.3 (30.8) | 16.3 (17.4) | **0.038\*** |
| Completeness of Resection | R0 | 121 (79.6) | 69 (94.5) | **0.015\*** | 104.8 (80.0) | 88.0 (94.3) | **0.014\*** |
|  | R1 | 30 (19.7) | 4 ( 5.5) |  | 25.2 (19.2) | 5.3 ( 5.7) |  |
|  | R2 | 1 ( 0.7) | 0 ( 0.0) |  | 1.0 ( 0.8) | 0.0 ( 0.0) |  |
| Pathological Complete Response (pCR) | | 11 (7.2) | 10 (13.7) | 0.188 | 10.0 (7.6) | 13.7 (14.6) | 0.131 |
| Data presented as absolute number (%) and median (IQR), \*<0.05, § χ2 test, except ¶ Mann–Whitney U test | | | | | | | |

**Table 4.** **Clinical and Pathological Outcomes before and after IPTW (SCC only)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Unadjusted Outcomes | | | Weighted Sample Outcomes | | |
|  |  | CT (n = 14) | CRT (n = 45) | p§ | CT (n = 35.0) | CRT (n = 24.2) | p§ |
| Complications | | 9 (64.3) | 31 (68.9) | 1.000 | 22.6 (64.7) | 16.6 (68.9) | 0.783 |
| Anastomotic Leak | | 2 (14.3) | 4 ( 8.9) | 0.938 | 6.1 (17.4) | 2.3 ( 9.6) | 0.470 |
| Pulmonary Complications | | 7 (50.0) | 12 (26.7) | 0.192 | 17.6 (50.3) | 6.5 (27.0) | 0.128 |
| Chyle Leak | | 0 ( 0.0) | 6 (13.3) | 0.350 | 0.0 ( 0.0) | 3.1 (12.7) | **0.004\*** |
| Length of Stay | | 14 [10, 17] | 11 [8, 14] | **0.046\*** | 14 [10, 19] | 11 [8, 13] | **0.019\*** |
| Return to Theatre | | 2 (14.3) | 6 (13.3) | 1.000 | 6.5 (18.5) | 3.4 (14.1) | 0.719 |
| Unplanned Escalation of Care | | 2 (14.3) | 4 ( 8.9) | 0.938 | 6.5 (18.5) | 2.0 ( 8.2) | 0.319 |
| Major Complication (CD3a-5) | | 4 (28.6) | 12 (26.7) | 1.000 | 10.0 (28.7) | 6.5 (26.7) | 0.892 |
| In Hospital Mortality | | 1 ( 7.1) | 1 ( 2.2) | 0.966 | 2.9 ( 8.3) | 0.6 ( 2.4) | 0.346 |
| ypT Stage | 0 | 2 (14.3) | 23 (51.1) | 0.107 | 2.5 ( 7.2) | 12.2 (50.4) | **0.003\*** |
|  | 1 | 1 ( 7.1) | 1 ( 2.2) |  | 3.1 ( 8.9) | 0.5 ( 2.2) |  |
|  | 2 | 1 ( 7.1) | 2 ( 4.4) |  | 2.1 ( 6.0) | 1.0 ( 4.3) |  |
|  | 3 | 10 (71.4) | 17 (37.8) |  | 27.3 (77.9) | 9.4 (39.0) |  |
|  | 4 | 0 ( 0.0) | 2 ( 4.4) |  | 0.0 ( 0.0) | 1.0 ( 4.2) |  |
| ypN Stage | 0 | 8 (57.1) | 36 (80.0) | **0.023\*** | 16.9 (48.3) | 19.4 (80.2) | 0.158 |
|  | 1 | 4 (28.6) | 9 (20.0) |  | 12.2 (34.9) | 4.8 (19.8) |  |
|  | 2 | 2 (14.3) | 0 ( 0.0) |  | 5.9 (16.8) | 0.0 ( 0.0) |  |
| Response to Neoadjuvant Therapy | TRG 1 | 2 (15.4) | 29 (64.4) | **<0.001\*** | 2.5 ( 7.9) | 15.3 (63.4) | **<0.001\*** |
|  | TRG 2 | 0 ( 0.0) | 5 (11.1) |  | 0.0 ( 0.0) | 2.9 (11.8) |  |
|  | TRG 3 | 0 ( 0.0) | 8 (17.8) |  | 0.0 ( 0.0) | 4.3 (17.8) |  |
|  | TRG 4 | 5 (38.5) | 2 ( 4.4) |  | 13.3 (41.5) | 1.1 ( 4.7) |  |
|  | TRG 5 | 6 (46.2) | 1 ( 2.2) |  | 16.2 (50.7) | 0.5 ( 2.3) |  |
| Vascular Invasion | | 2 (14.3) | 9 (20.0) | 0.931 | 6.3 (18.1) | 4.8 (19.8) | 0.899 |
| Completeness of Resection | R0 | 11 (76.9) | 40 (88.9) | 0.519 | 26.6 (75.6) | 21.4 (88.4) | 0.275 |
|  | R1 | 3 (23.1) | 5 (11.1) |  | 8.4 (24.4) | 2.8 (11.6) |  |
| Pathological Complete Response (pCR) | | 2 (14.3) | 21 (46.7) | 0.063 | 2.5 ( 7.2) | 11.1 (46.1) | **0.005\*** |
| Data presented as absolute number (%) and median (IQR), \*<0.05, § χ2 test, except ¶ Mann–Whitney U test | | | | | | | |

**Appendix 1. Clinical and Pathological Outcomes before and after IPTW**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Unadjusted Outcomes** | | | **Weighted Sample Outcomes** | | |
|  |  | **CT (n = 166)** | **CRT (n = 118)** | **p§** | **CT (n =166.0)** | **CRT (n =117.5)** | **p§** |
| **Complications** |  | 107 (64.5) | 76 (64.4) | 1.000 | 107.7 (64.9) | 74.3 (63.3) | 0.807 |
| **Anastomotic Leak** |  | 10 ( 6.0) | 8 ( 6.8) | 0.992 | 13.0 ( 7.8) | 6.6 ( 5.6) | 0.526 |
| **Pulmonary Complications** |  | 66 (39.8) | 35 (29.7) | 0.104 | 68.7 (41.4) | 37.3 (31.8) | 0.159 |
| **Chyle Leak** |  | 7 ( 4.2) | 12 (10.2) | 0.082 | 6.0 ( 3.6) | 13.6 (11.6) | **0.017\*** |
| **Length of Stay** |  | 11 [8, 15] | 9 [8, 12] | 0.076¶ | 11 [8, 15] | 9 [8, 12] | **0.007\*** ¶ |
| **Return to Theatre** |  | 16 ( 9.6) | 11 ( 9.3) | 1.000 | 17.5 (10.5) | 11.2 ( 9.6) | 0.833 |
| **Unplanned Escalation of Care** |  | 22 (13.3) | 17 (14.4) | 0.918 | 23.2(14.0) | 19.5 (16.6) | 0.622 |
| **Major Complication (CD3a-5)** |  | 40 (24.1) | 28 (23.7) | 1.000 | 39.9 (24.0) | 27.7 (23.6) | 0.943 |
| **In Hospital Mortality** |  | 1 ( 0.6) | 2 ( 1.7) | 0.765 | 2.9 ( 1.8) | 1.6 ( 1.4) | 0.837 |
| **ypT Stage** | **0** | 14 ( 8.4) | 39 (33.1) | **<0.001\*** | 13.5 ( 8.1) | 32.1 (27.3) | **0.002\*** |
|  | **1** | 40 (24.1) | 17 (14.4) |  | 35.9 (21.6) | 18.2 (15.5) |  |
|  | **2** | 24 (14.5) | 15 (12.7) |  | 23.3 (14.1) | 18.7 (15.9) |  |
|  | **3** | 86 (51.8) | 45 (38.1) |  | 91.8 (55.3) | 47.5 (40.5) |  |
|  | **4** | 2 ( 1.2) | 2 ( 1.7) |  | 1.5 ( 0.9) | 1.0 ( 0.9) |  |
| **ypN Stage** | **0** | 86 (51.8) | 71 (60.2) | **0.008\*** | 85.4 (51.4) | 65.4 (55.7) | 0.115 |
|  | **1** | 32 (19.3) | 31 (26.2) |  | 36.2 (21.8) | 29.7 (25.2) |  |
|  | **2** | 29 (17.5) | 14 (11.9) |  | 27.9 (16.8) | 20.3 (17.3) |  |
|  | **3** | 19 (11.4) | 2 ( 1.7) |  | 16.5 (10.0) | 2.0 ( 1.7) |  |
| **Response to Neoadjuvant Therapy** | **TRG 1** | 18 (11.0) | 43 (36.4) | **<0.001\*** | 16.9 (10.4) | 33.1 (28.2) | **<0.001\*** |
|  | **TRG 2** | 27 (16.5) | 29 (24.6) |  | 23.3 (14.4) | 34.7 (29.5) |  |
|  | **TRG 3** | 20 (12.2) | 25 (21.2) |  | 16.7 (10.3) | 25.9 (22.1) |  |
|  | **TRG 4** | 47 (28.7) | 17 (14.4) |  | 50.0 (30.9) | 19.9 (16.9) |  |
|  | **TRG 5** | 48 (29.3) | 4 ( 3.4) |  | 52.0 (32.1) | 3.8 ( 3.3) |  |
|  | **Not assessed** | 4 ( 2.4) | 0 ( 0.0) |  | 3.1 ( 1.9) | 0.0 ( 0.0) |  |
| **Vascular Invasion** |  | 49 (29.5) | 23 (19.5) | 0.076 | 46.6(28.1) | 21.0 (17.9) | 0.074 |
| **Completeness of Resection** | **R0** | 131 (79.4) | 109 (92.4) | **0.010\*** | 130.8 (79.1) | 109.3 (93.1) | **0.009\*** |
|  | **R1** | 33 (20.0) | 9 ( 7.6) |  | 33.6 (20.3) | 8.1 ( 6.9) |  |
|  | **R2** | 1 ( 0.6) | 0 ( 0.0) |  | 1.0 ( 0.6) | 0.0 ( 0.0) |  |
| **Pathological Complete Response (pCR)** | | 13 (7.8) | 31 (26.3) | <0.001\* | 12.5 (7.5) | 24.8 (20.9) | 0.002\* |
| Data presented as absolute number (%) and median (IQR), \*<0.05, § χ2 test, except ¶ Mann–Whitney U test | | | | | | | |