TRANSHIATAL ESOPHAGECTOMY IS NOT ASSOCIATED WITH POOR QUALITY LYMPHADENECTOMY

Esofagectomia trans-hiatal não está associada com linfadenectomia de baixa qualidade

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ABSTRACT – Background: Esophageal cancer neoadjuvant therapy followed by surgery increases the likelihood of treatment success. Aim: To evaluate variables that can influence the number of retrieved lymph nodes, the number of retrieved metastatic lymph nodes and lymphnodal recurrence in esophagectomy after neoadjuvant chemoradiotherapy. Methods: Patients of a single institute were evaluated after completion of trimodal therapy. Univariate and multivariate analyses were performed to evaluate variables that can influence in the number of retrieved lymph nodes and retrieved metastatic lymph nodes. Results: One hundred and forty-nine patients were included. Thorascopy access was considered an independent factor for the number of lymph nodes retrieved, but was neither related to the number of positive lymph nodes retrieved nor to lymphnodal recurrence. Pathological complete response on the primary tumor site did not statistically influence the likelihood of a lower number of lymph nodes retrieved. Conclusion: Patients submitted to esophagectomy after neoadjuvant chemoradiotherapy, thoracoscopic access is more accurate for pathological staging, even in a complete pathological response. With a proper patient selection, transhiatal surgery may preserve the quality of lymphadenectomy of the positive lymph nodes.

INTRODUCTION

Esophageal cancer is a growing health issue expected to increase in incidence over the next years due to the upsurge of gastroesophageal reflux disease and obesity. It is still a challenging disease with a poor prognosis despite the advances in chemoradiotherapy and all the progress made in the last years in minimally invasive surgery and postoperative management.

The prognosis of this aggressive neoplasm depends mainly on the local invasion extension, hematogenous metastasis, and lymphatic spread. Surgical resection is the primary treatment for localized esophageal carcinoma, and a properly lymphadenectomy is crucial for long-term survival. Both the number of lymph nodes retrieved during esophagectomy and the metastatic lymph correlated with survival rates. Also, lymph node status is crucial for neoplasm staging and, thus, for establishing prognosis and treatment strategies.
On the other hand, good quality lymphadenectomy may be challenging after chemoradiation, once it leads to the formation of fibrosis inside the radiation field. Also, systemic neoadjuvant chemotherapy may modify the number and the distribution of mediastinal lymph nodes and also affect metastatic lymph nodes. At the same time, neoadjuvant chemoradiation therapy is the standard treatment for most localized esophageal neoplasms, once it can improve long-term survival by controlling of locoregional disease, tumor downstaging before surgery, and targeting micrometastases, decreasing the risk of distant metastasis.

This retrospective cohort study aims to evaluate the variables that can influence the quality of lymphadenectomy in esophagectomy after neoadjuvant chemoradiation therapy using platinum- and taxane-based regimen. For lymphadenectomy quality assessment, this study evaluated the number of lymph nodes retrieved (LNr), the number of positive lymph nodes retrieved (PLNr), and lymphnodal recurrence rate.

**METHODS**

This study was approved by institutional ethics committee with number 3.315.331

**Study design**

This is a retrospective cohort in which patients of a single institute with completion of neoadjuvant chemoradiotherapy using platinum- and taxane-based regimens, followed by curative intent esophagectomy, were selected. Radiation dose ranged from 41.4 to 50.4 cGy. A transthoracic approach with two-field lymph-node dissection was performed for tumors extending proximally to the tracheal bifurcation. A transhiatal resection was preferred for tumors involving the esophagogastric junction. Patients were recruited from 2009 to 2019, and were staged with endoscopy, CT-scan, and PET-Scan before neoadjuvant therapy and classified according to the 8th edition of UICC staging. Patients were followed with clinical exams, endoscopies, and CT-scans. The endpoints evaluated were the number of lymph nodes retrieved (LNr), the number of positive lymph nodes retrieved (PLNr), and lymphnodal recurrence rate.

**RESULTS**

Were enrolled 149 consecutive patients between 2009 and 2019 that have undergone neoadjuvant chemoradiotherapy using platinum- and taxane-based regimen followed by curative intent esophagectomy. The mean age was 61.5 years (SD±8.1), with male predominance (76%). There were 101 squamous cell carcinoma (SCC) and 48 esophageal adenocarcinoma patients. The mean follow-up was 31.3 months (SD±22).

The median number of lymph nodes retrieved (LNr) was 19. Patients were grouped as up to 19 and more than 19 LN for univariate analysis (Table 1). Surgical access (p<0.001) and age (p=0.003) influenced the number of LNr in esophagectomy. Pathological complete response (pCR) on the primary tumor site did not statistically influence the likelihood of a lower number of LNr (OR 0.81; 95%CI: 0.41-1.56; p=0.536). When analyzing each surgical access separately (transhiatal or thoracoscopy), pCR was still not statistically associated with the number of LNr (Table 2). In multiple regression analysis, only thoracoscopy access was considered an independent factor (OR 6.4; 95%CI: 2.18-18.75; p=0.001).

The number of positive lymph nodes retrieved (PLNr)

| Variable                                      | Lymph node retrieved | OR   | CI (95%) | P     |
|-----------------------------------------------|----------------------|------|----------|-------|
|                                               | ≤19 (n=76)           | >19 (n=73) |         |       |
| Gender, n (%)                                 |                      |      |          | 0.807 |
| Male                                          | 57 (50.4)            | 56 (49.6) | 1.00    |       |
| Female                                        |                      |      |          |       |
| Histology, n (%)                              |                      |      |          | 0.856 |
| SCC                                           | 51 (50.5)            | 50 (49.5) | 1.00    |       |
| Adenocarcinoma                                |                      |      |          |       |
| Surgical access, n (%)                        |                      |      |          | <0.001|
| Transhiatal                                   | 27 (84.4)            | 5 (15.6)  | 1.00    |       |
| Thoracoscopy                                  | 49 (41.9)            | 68 (58.1) | 7.49    | 2.70  |
| cStage, n (%)                                 |                      |      |          | 0.174 |
| I/II                                          | 23 (60.5)            | 15 (39.5) | 1.00    |       |
| III/IV                                        | 53 (47.7)            | 58 (52.3) | 1.68    | 0.79  |
| Grade of cellular differentiation, n (%)      |                      |      |          | 0.370 |
| Well                                          | 9 (69.2)             | 4 (30.8)  | 1.00    |       |
| Moderately                                    | 47 (48.5)            | 50 (51.5) | 2.39    | 0.69  |
| Poorly                                        | 18 (50)              | 18 (50)   | 2.25    | 0.59  |
| pCR, n (%)                                    |                      |      |          | 0.536 |
| No                                            | 42 (48.8)            | 44 (51.2) | 1.00    |       |
| Yes                                           | 34 (54)              | 29 (46)   | 0.81    | 0.41  |
| Age (years)                                   |                      |      |          | 0.003**|
| median (min; max)                             | 63 (42;79)           | 60 (37;76) | 0.941  | 0.904 |
| Interval CRT-surgery (days)                   |                      |      |          | 0.169**|
| median (min; max)                             | 96 (38;288)          | 94 (31;293) | 0.995  | 0.987 |

Chi-squared test **Mann-Whitney
was associated with gender (p = 0.044), adenocarcinoma histology (p < 0.001), and pCR on the primary tumor site (p < 0.001) on univariate analysis (Table 3). In the multiple regression analysis, pCR on the primary tumor (OR: 0.1; 95% CI: 0.04-0.25; p < 0.001) and gender (male patients were more likely to have PLN r than women (OR: 2.69; 95% CI: 1.03-7.04; p = 0.044) were independent variables associated with the number of PLN r. Surgical access was not related to PLN r.

Concerning lymph nodal recurrence, only pCR of the primary tumor was statistically significant (OR: 0.327; 95% CI: 0.08-0.99; p = 0.038, Table 4). The surgical access was not related to lymph nodal recurrence.

### TABLE 3 – Univariate analysis for metastatic lymph nodes

| Variable                        | Metastatic lymph node (%) | OR   | CI (95%) | p     |
|--------------------------------|---------------------------|------|---------|-------|
|                                | No (n=86)                 |      |         |       |
|                                | Yes (n=63)                |      |         |       |
| Gender, n (%)                  |                           | Lower|         |       |
| Male                           | 67 (59.3)                 | 46 (40.7) | 1.00 | 0.044 |
| Female                         | 28 (77.8)                 | 8 (22.2)  | 0.42 |       |
| Histology, n (%)               |                           |      |         |       |
| SCC                            | 74 (73.3)                 | 27 (26.7) | 1.00 | <0.001|
| Adenocarcinoma                 | 21 (43.8)                 | 27 (56.3) | 3.52 |       |
| Surgical access, n (%)         |                           |      |         |       |
| Transhiatal                    | 20 (62.5)                 | 12 (37.5)  | 1.00 | 0.867 |
| Thoracoscopy                   | 75 (64.1)                 | 42 (35.9) | 0.93 |       |
| cStage, n (%)                  |                           |      |         |       |
| I/II                           | 28 (73.7)                 | 10 (26.3)  | 1.00 | 0.323#|
| III/IV                         | 67 (60.4)                 | 44 (39.6) | 1.84 |       |
| Grade of cellular differentiation, n (%) |                   |      |         | 0.001 |
| Well                           | 8 (61.5)                  | 5 (38.5)   | 1.00 |       |
| Moderately                     | 65 (67)                   | 32 (33)    | 0.79 |       |
| Poorly                         | 19 (52.8)                 | 17 (47.2)  | 1.43 |       |
| pCR, n (%)                     |                           |      |         |       |
| No                             | 39 (45.3)                 | 47 (54.7)  | 1.00 | <0.001|
| Yes                            | 56 (88.9)                 | 7 (11.1)    | 0.10 | 0.05  |
| Age (yr)                       |                           |      |         | 0.298**|
| median (min; max)              | 63 (41;79)                | 61 (37;78) | 0.97 |       |
| Interval CRT-surgery (days)    |                           |      |         | 0.912**|
| median (min; max)              | 94 (36;293)               | 98 (31;244) | 0.99 |       |

Chi-squared test **Mann-Whitney test

### TABLE 4 – Univariate analysis for lymph nodal recurrence

| Variable                        | Lymph nodal recurrence | HR   | CI 95% | p     |
|--------------------------------|------------------------|------|--------|-------|
|                                | No (n=126)             |      |        |       |
|                                | Yes (n=23)             |      |        |       |
| Gender, n (%)                  |                         |lower|        |       |
| Male                           | 97 (85.8)               | 16 (14.2) | 1.00 | 0.53  |
| Female                         | 29 (80.6)               | 7 (19.4)    | 1.32 |       |
| Histology, n (%)               |                         |      |        |       |
| SCC                            | 41 (85.4)               | 7 (14.6)    | 1.00 | 0.53  |
| Adenocarcinoma                 | 85 (84.2)               | 16 (15.8)   | 1.01 | 0.53  |
| Surgical access, n (%)         |                         |      |        |       |
| Transhiatal                    | 30 (93.8)               | 2 (6.3)     | 1.00 | 0.98  |
| Thoracoscopy                   | 96 (82.1)               | 21 (17.9)    | 2.91 |       |
| cStage, n (%)                  |                         |      |        | 0.038 |
| I/II                           | 32 (84.2)               | 6 (15.8)     | 1.00 |       |
| III/IV                         | 94 (84.7)               | 17 (15.3)    | 0.98 | 0.97  |
| pCR                            | 58 (92)                 | 5 (8)      | 0.327|       |
| Grade of cellular differentiation, n (%) |                   |      |        | 0.038 |
| I                              | 10 (76.9)               | 3 (23.1)     | 1.00 |       |
| II                             | 82 (84.5)               | 15 (15.5)    | 0.863|       |
| III                            | 31 (86.1)               | 5 (13.9)     | 0.945|       |
| Age (yr)                       |                         |      |        |       |
| Mean±SD                        | 61±8.6                 | 58.6±8.4   | 1.00 |       |
| Median (min; max)              | 62.5 (41; 79)           | 60 (37.71) | 1.00 | 0.49  |

Chi-squared test

**Table 2 – There was no association of lymph node retrieved and pathological complete response (pCR)**

| Lymph node retrieved | Total | p     |
|----------------------|-------|-------|
| Thoracoscopy         |       |       |
| ≤19                  | 26 (39.4) | 40 (60.6) | 66 | 0.535 |
| >19                  | 23 (45.1) | 28 (54.9) | 51  |
| Transhiatal          |       |       |
| ≤19                  | 16 (80) | 4 (20)  | 20  | 0.626 |
| >19                  | 11 (91.7) | 1 (8.3)  | 12  |

Fisher’s exact test Fisher’s exact test

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**TRANSHIATEAL ESOPHAGECTOMY IS NOT ASSOCIATED WITH POOR QUALITY LYMPHADENECTOMY**
This cohort comprising 149 patients submitted to neoadjuvant chemoradiotherapy using platinum- and taxane-based regimen followed by curative intent esophagectomy showed that thoracoscopic access was more likely to achieve lymph node retrieval than transthiatal access. On the other hand, surgical access did not differ in the number of positive lymph nodes retrieved, and also did not influence the risk for lymphnodal recurrence.

The transthoracic access provides a better pathological staging since it showed a higher number of LNr. However, the number of LNR is not the same for the good quality lymphadenectomy. In fact, with proper patient selection, transthiatal access with infracarinal lymphadenectomy may be enough to retrieve the nodal stations with a higher risk for positivity, avoiding lymphnodal recurrence. In this scenario, transtial approach turns to be a good option, since it is associated with reduced perioperative morbidity, a shorter hospital stay, and decreased in-hospital mortality rates.11,13, mainly in the cases of laparoscopic transhiatal esophagectomy12.

Neither complete pathological response nor histological type was associated with the number of retrieved lymph nodes. Therefore, the number of LNR should be taken into consideration as one of the parameters when monitoring the quality of esophagectomy for cancer after neoadjuvant therapy, regardless of pathological response to neoadjuvant therapy or histological type. This finding differs from rectal cancer, in which pCR after chemoradiotherapy is associated with a lower number of lymph nodes harvested. Squamous cell carcinoma showed a higher likelihood of a lower number of positive lymph nodes retrieved, but this is probably due to the higher response to neoadjuvant therapy.

Gender was associated with a higher likelihood of PLNr. While the mechanism underlying the association of lymph nodes metastasis and gender, epidemiological studies have reported a potential association between gender hormones and certain neoplasms, such as colorectal and thyroid cancers.10,11.

This study has several limitations. It was a retrospective, nonrandomized, single-institution; the number of patients, especially with adenocarcinoma, was relatively small; and different neoadjuvant chemotherapy other than platinum- and taxane-based regimen, were not evaluated. Further studies with large controlled trials, comparing transthiatal and transthoracic access patients are required.

CONCLUSION

Thoracoscopic access is more accurate for pathological staging in patients submitted to esophagectomy after neoadjuvant chemoradiotherapy using platinum- and taxane-based regimen, even for a complete pathological response. With proper selection, transthiatal surgery may preserve the quality of lymph node excision of the positive lymph nodes.

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