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1 **Prognostic value of elective neck dissection in adenoid cystic carcinoma of**
2 **head and neck: A meta-analysis. A call for randomised trial and**
3 **international consensus**

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25 **Running heads:** Elective neck dissection in adenoid cystic carcinoma of head and neck

26 **ABSTRACT**

27 Adenoid cystic carcinoma of head and neck (AdCCHN) is uncommon salivary gland cancer
28 characterised for infrequent neck metastases, high rate of local and distant recurrence. The
29 aim of this meta-analysis was to analyse significance of elective neck dissection (END) in
30 terms of overall survival (OS) in patients with AdCCHN. A systematic literature search and
31 meta-analysis was performed. Endpoint assessed by this meta-analysis included 5-year OS
32 (death from any cause). Statistical heterogeneity was assessed using the Cochrane Q test and
33 I^2 statistic. A pooled odds ratio (OR) was reported with 95% confidence interval (CI). There
34 were 1934 patients in END arm and 3083 in the observation group. The pooled OR,
35 calculated for END vs. observation, was 0.94. Patients receiving END had similar risk for
36 death compared to observation cohort (P=0.76). No significant difference in final outcome
37 after patient's stratification based on T stage was identified (OR for T1/T2 1.27, P=0.39; OR
38 for T3/T4 0.95, P=0.90). Observation for cN0 neck is a reasonable option in AdCCHN. This
39 findings suggest conduction of prospective trials on indications and extent of END in
40 AdCCHN.

41

42 **Keywords:** head and neck cancer; carcinoma, adenoid cystic; neck dissection; neck
43 metastases; survival

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45

46 **INTRODUCTION**

47 Adenoid cystic carcinoma of head and neck (AdCCHN) is a rare, slow growing, malignant
48 epithelial tumor, comprising about 1% of all head and neck malignancies and about 10-15%
49 of all salivary gland neoplasms.¹ This tumor is known for its slow progression accompanied
50 with perineural invasion (PNI), rare lymphatic spread to the neck, high rate of local
51 recurrence and delayed occurrence of distant metastases.

52 Whereas therapeutic neck dissection (TND) is performed in all clinically node-positive (cN+)
53 patients, management of cN0 neck is still controversial and elective neck dissection (END) is
54 not routinely carried out in patients with AdCCHN. While isolated lymph node involvement
55 may not have significant effect on survival, it is a risk factor for subsequent development of
56 distant metastases.² Recently, we reported largest systematic review on END in AdCCHN
57 analysing important features of cN0 treated neck (incidence of occult neck metastases, lowest
58 involved region, extranodal extension (ENE), the role of sublocalization with respect to
59 regional metastases etc.).³ The aim of this meta-analysis was to further address these
60 important issues and to determine impact of prophylactic neck management in patients with
61 AdCCHN with respect to survival. Additional effort was done in order to determine
62 prognostic value of END based on the T stage of the primaries (early vs advanced disease).
63 To our knowledge this is first meta-analysis of the role of END in AdCCHN.

64

65 **MATERIALS AND METHODS**

66 Inclusion criteria were: (1) diagnosis of AdCCHN, (2) studies with patients undergoing
67 primary surgical treatment including END group and those being observed for the cN0 neck,
68 (3) information on OS rates among examined arms (END vs observation). Based on our
69 previous article on END in AdCCHN,³ preliminary analysis identified 1490 AdCCHN studies
70 with five reports which met criteria mentioned above. Study by Lee et al.⁴ was excluded due
71 to fact that survival analysis was done comparing overall N+ rates vs N0 AdCCHN.
72 Difference in OS between END vs no END group was not found (p=0.178), however there
73 were no survival curves or absolute numbers on which analysis could be done. Also,
74 additional search was done covering period between the date of last search (August 5, 2019)
75 and July 25, 2020. One of the additionally identified studies (N=106) met these criteria.
76 Therefore, five studies with 5017 patients were included in the final meta-analysis (**Table**
77 **1**).⁵⁻⁹

78
79 ***Statistical analysis***

80 Endpoint assessed by this meta-analysis included 5-year OS (death from any cause) Statistical
81 heterogeneity was assessed using the Cochrane Q test and I^2 statistic. Statistically significant
82 heterogeneity was considered present at $P < 0.10$ and $I^2 > 50\%$. When homogeneity was
83 minimal ($P \geq 0.10$, $I^2 \leq 50\%$), a fixed-effects model was applied for meta-analysis of disease
84 outcome (OS); otherwise, a random effects model was used. Egger's test was used to estimate
85 potential publication bias. A pooled odds ratio (OR) was reported with 95% confidence
86 interval (CI). Analyses were conducted using statistical software Stats Direct version 3.0.165
87 (Stats Direct Ltd., Altrincham, United Kingdom).

88

89

90 **RESULTS**

91 This meta-analysis included four studies with a total of 5017 AdCCHN patients undergoing
92 END in 1934 cases, while 3083 patients have been observed for cN0 neck. Included studies
93 are presented in **Table 1**. There were 315 deaths from any cause in END group at 5-year
94 follow-up, while 564 deaths were reported in the observation cohort at the same time period.
95 **Table 2** shows patient's demographic and clinical characteristics.

96

97 ***5-year OS (all stages AdCCHN)***

98 The analysis of pooled studies showed significant heterogeneity ($I^2=74.3\%$, Cochran
99 $Q=15.59$, $P=0.004$) without publication bias (Egger: bias= 0.21, $P=0.93$) (**Figure 1**).

100 Therefore, the random effect model was used. The data from five studies were available for
101 the analysis of 5-year OS (**Figure 2**). There were 1934 patients in the END group and 3083
102 patients in the observation group. The pooled OR, calculated for END vs. observation, was
103 0.94 (95% CI, 0.63- 1.40; $P=0.76$).

104

105 ***5-year OS (early vs advance stage AdCCHN)***

106 **Early AdCCHN**

107 The analysis of pooled studies showed significant heterogeneity ($I^2=61.1\%$, Cochran $Q=2.57$,
108 $P=0.11$). Therefore, the random effect model was used. Due to small number of patients bias
109 indicator could not be calculated. The data from two studies were available for the analysis of
110 5-year OS (**Figure 3**). There were 579 patients in the END group and 1469 patients in the
111 observation group. The pooled OR, calculated for END vs. no END, was 1.27 (95% CI 0.74 -
112 2.16; $P=0.39$).

113

114

115 **Advanced AdCCHN**

116 The analysis of pooled studies showed significant heterogeneity ($I^2=79.6\%$, Cochran $Q=4.89$,
117 $P=0.03$). Therefore, the random effect model was used. Due to small number of patients bias
118 indicator could not be calculated. The data from two studies were available for the analysis of
119 5-year OS (**Figure 4**). There were 345 patients in the END group and 903 patients in the
120 observation group. The pooled OR, calculated for END vs. no END, was 0.95 (95% CI 0.43 -
121 2.09; $P=0.90$).

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126 **DISCUSSION**

127 AdCCHN accounts for 3-5% of all head and neck malignancies. It's characterized by
128 intermediate grow rate, low probability of regional lymphatic involvement and frequent
129 distant metastases/local recurrences.

130 Whereas TND is performed in all cN+ patients, management of cN0 neck is still controversial
131 and END is not routinely carried out in patients with AdCCHN. The decision regarding END
132 performance should be based on both the incidence of occult lymph node metastases as well
133 as expected impact of applied treatment on survival. Given the lack of data on incidence of
134 neck metastases and it's influence on final outcome, the association between occult neck
135 disease and OS remain inconclusive. The main objective of this study was to determine
136 impact of END on survival in order to guide indications for prophylactic neck treatment in
137 AdCCHN patient's.

138 Previously, we have published an article on important features among AdCCHN patients
139 undergoing END.³ In the largest systematic review on the examined topic, we analysed 18
140 studies with a total of 5767 AdCCHN undergoing END in 2450 cases. According to our
141 results elective lymphadenectomy was employed in 42.5% of patients with AdCCHN (range
142 9.2 - 100 %) and the overall rate of occult neck metastases was reported to range between 0%
143 and 43.7%, the average being 13.9%. However, no meta-anaylsis on END and survival was
144 performed due to high heterogeneity among examined studies. Also, there are no published
145 meta-analysis on this topic: one meta-analysis combined both TNDs and ENDs as one clinical
146 setting which makes these results and recommendations questionable,¹⁰ while other analysed
147 other features of this tumor (molecular mutations, chromosomal abberations, lymphovascular
148 and perineural invasion). Additionally, no randomised trial on this topic has been conducted
149 to date.

150 Given the fact that OS is the single most important feature of any relevant trial in oncology
151 when examining potential efficacy of therapy, we decide to explore this end-point in cohort of
152 AdCCHN undergoing END. In this meta-analysis, control group was consisted of AdCCHN
153 patients with identical disease stage (cN0) being observed for the neck.
154 According to the results of this meta-analysis, observation of the cN0 neck is a rationale
155 option for AdCCHN patients with cN0 irrespectively of T stage. It's seems that END is not
156 associated with survival benefit in any subgroup of patients having this rare tumour.
157 Rational explanation for this findings could be found in biological behaviour of AdCCHN.
158 While neck metastases in vast majority of head and neck carcinomas are the single most
159 important prognosticator of poorer outcome, this survival disadvantage may be less prominent
160 is AdCCHN due to indolent course of this tumour. Additonal explanation could be potential
161 higher rates of elective neck irradiation in observation cohort resulting in similar neck control
162 compared to those achieved by neck surgery. However, most historical data analysing
163 postoperative irradiation showed that this modality reduces local recurrence rates without
164 influencing final outcome.^{5,11} Furthermore, in this study patients within END group
165 underwent adjuvant radiotherapy more often (absolute difference 5.7%) compared to no END
166 cohort. On the contrary, insufficient data on adjuvant radiotherapy features (included regions,
167 dose distribution, whether field covered the neck electively in observation cohort, included
168 field in END group with/without occult neck metastases) make it impossible to draw clear
169 conclusions on its role in cN0 setting. Also, in this meta-analysis observation group had less
170 favorable tumor/treatment related characteristics (almost half of the cases were minor
171 salivary gland AdCC and radiotherapy was less used), while other variables were comparable
172 (age, gender and T1/T2 stage disease) which probably exclude possibility of selection more
173 favorable patients in the group in which END was omitted.

174 The main weakness of the analysis is the non-randomised design of included studies. Due to
175 the lack of randomisation, the groups could vary in terms of characteristics associated with
176 outcomes. While our results (i.e. **Table 2**) show differences between groups for major
177 salivary glands there could also be differences for other variables not reported by this study.
178 As with any analysis of studies of this design, the size of differences between groups could be
179 confounded by other variables.

180 Additionally, publication, availability, and selection biases are a potential concern for meta-
181 analyses, but many reviewers neglect to examine or discuss them.¹² Reviewers should seek
182 individual participant data from all studies identified by a systematic review; include, where
183 possible, aggregate data from any studies lacking individual participant data to consider their
184 potential impact; and investigate funnel plot asymmetry.¹²

185 Also, these results must be taken with caution due to high heterogeneity of the data. Another
186 weakness of this study was no stratification among END and no END subgroup based to the T
187 stage (only two studies had this information) or histological subtype of the AdCCHN with
188 respect to survival which could influence obtained results.

189 Also, AdCCHN is not a homogenous entity and it does behave differently in its propensity to
190 metastasize to the neck from different sites. Although, survival was not associated with any
191 subgroup of patients we were not able to subdivide patients by site due to insufficient data
192 from individual studies. It's well known that there are subsites with higher risk of occult neck
193 metastases which could potentially benefit from END (i.e. floor of mouth and tongue
194 primaries with higher T stage). Whether in this subpopulation END actually affects survival
195 may never be able to be proven given the small numbers from published series.

196 According to this meta-analysis, although END is reported to provide staging information and
197 is associated with a prolonged regional control, it does not affect survival. Despite the fact
198 that neck status is the most important prognosticator in vast majority of the head and neck

199 malignancies, commonest pattern of recurrence and death among AdCCHN patients are
200 distant metastases and/or local recurrence. To date, only one study demonstrated survival
201 benefit of END being observed in a cohort of patients with advanced stage major salivary
202 gland (MSG) AdCC, with the effect being most pronounced in those undergoing adjuvant
203 radiotherapy (8% difference in survival between END vs observation group and absolute
204 improvement in survival of 11.5% at 5-year in those receiving adjuvant irradiation compared
205 to END alone).⁸ However, subgroup analysis showed that observation cohort had higher
206 percentage of minor salivary gland primaries (56.5% vs. 24.8%) which is sublocalization
207 associated with poorer survival compared to the similar stage MSG AdCC.

208 In conclusion, it seems that initially cN0 neck should be rather observed for neck recurrence
209 than treated "upfront" with prophylactic surgery of the neck. Most of the observed patients do
210 not develop regional metastases during follow-up period making END questionable in terms
211 of prognosis. This meta-analysis suggest conduction of prospective trial with balanced
212 experimental and control arm in terms of other prognostic factors (age, gender,
213 sublocalization of the primary, T stage, adjuvant radio(chemo)therapy, histological subtype
214 of the AdCCHN etc.) and international consensus on the neck treatment in cN0 setting in
215 order to assess it's role and treatment planning in AdCCHN patients.

216

217 **Declarations**

218 **Funding:** No funding

219 **Competing Interests:** Authors have no conflict of interest to declare.

220 **Ethical Approval:** All procedures performed in studies involving human participants were in
221 accordance with the ethical standards of the institutional and/or national research This is a
222 meta-analysis of retrospective studies which were conducted on already available data for

223 which formal consent was obtained. Therefore, institutional ethical approval was not required
224 according on the law and the national ethical guidelines.

225 **Patient Consent:** Patient consent was not required due to the fact that this is a meta-analysis
226 of retrospective studies for which formal consent was obtained. Furthermore, personal details
227 of patients are not known/available/included in any part of the paper and/or any
228 supplementary materials.

229

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270 **Figure legends**

271 Figure 1. Bias assessment plot for five-year OS

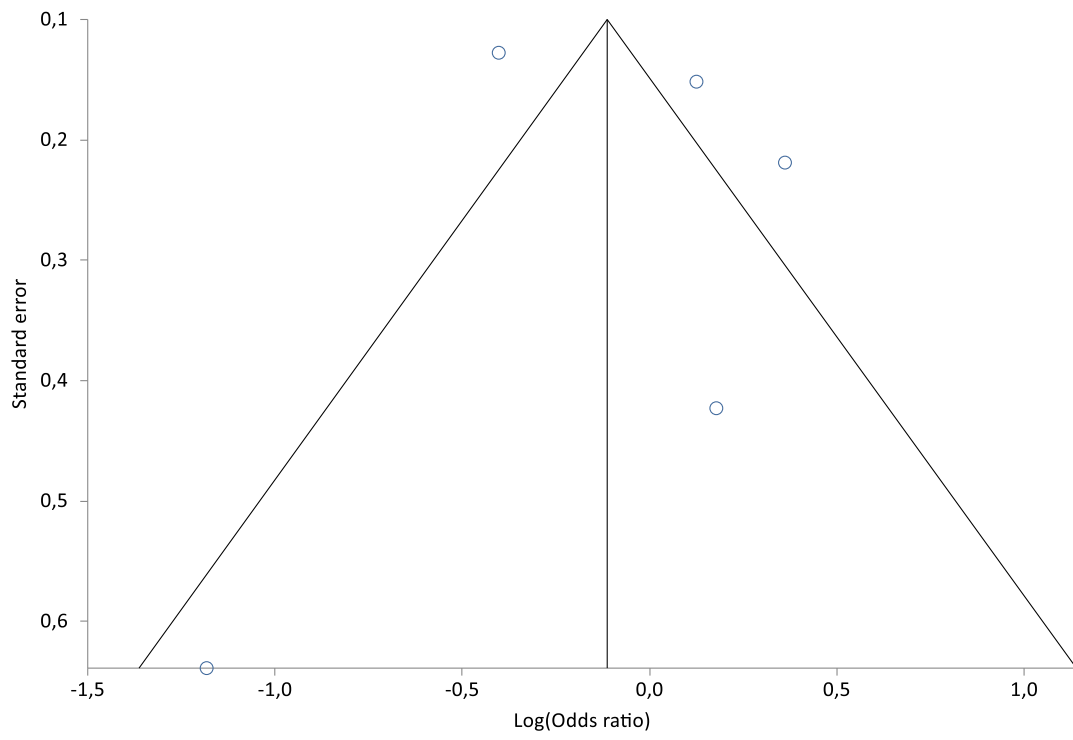
272 Figure 2. Meta-analysis of five-year OS (all-stages patients)

273 Figure 3. Meta-analysis of five-year OS (early-stage AdCCHN)

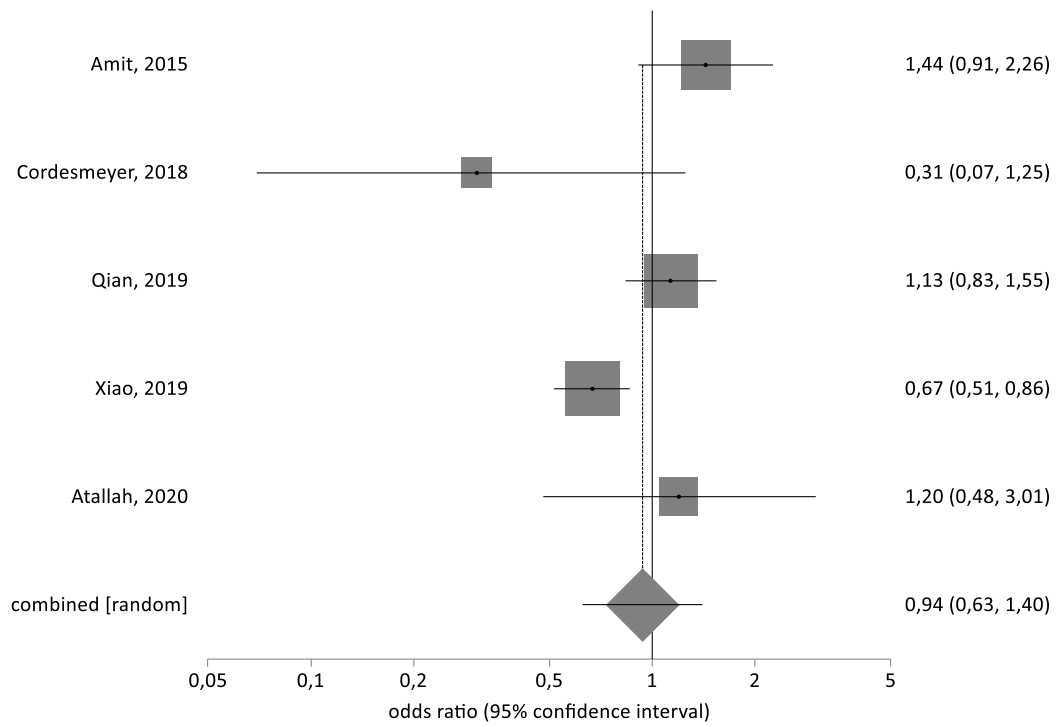
274 Figure 4. Meta-analysis of five-year OS (advanced-stage AdCCHN)

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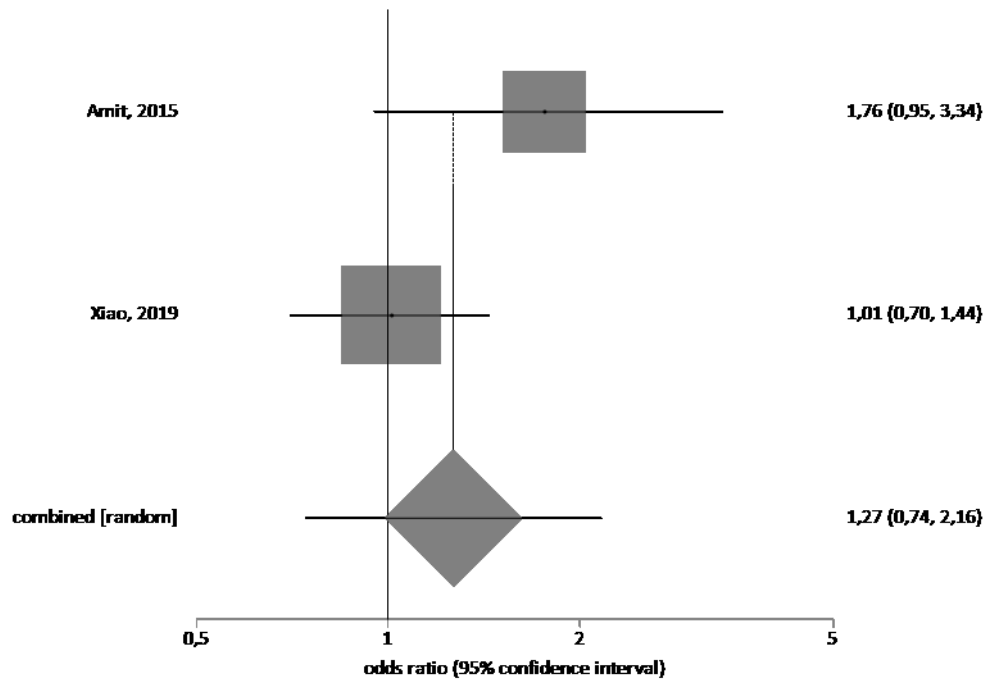
Bias assessment plot



Odds ratio meta-analysis plot [random effects]



Odds ratio meta-analysis plot [random effects]



Odds ratio meta-analysis plot [random effects]

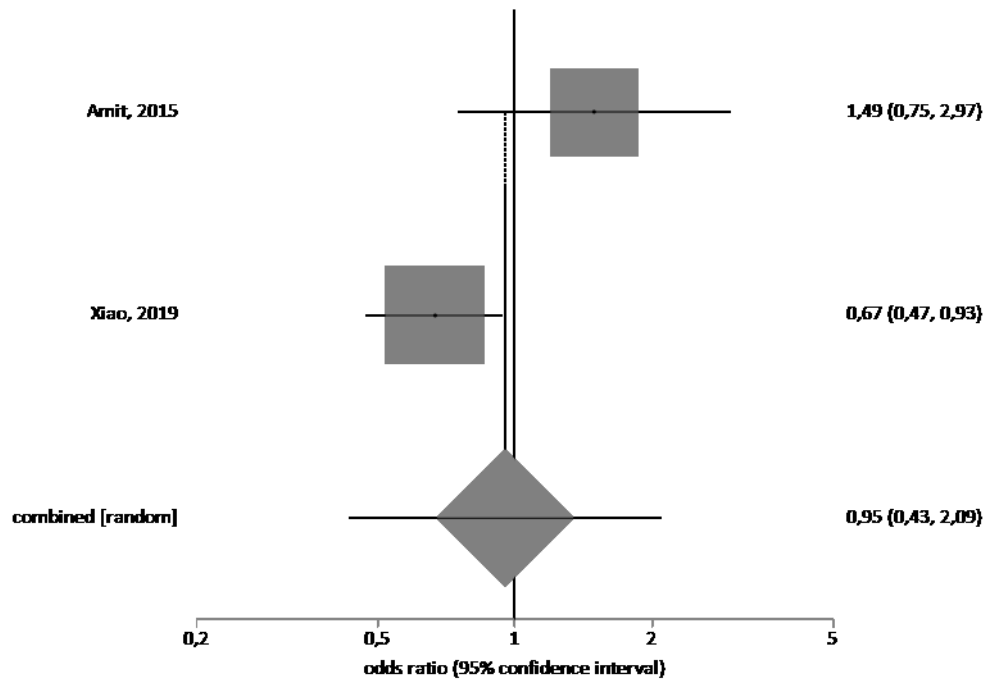


Table 1. Occult neck metastases in patients with HNAdCC.

Author (year)	No. of patients	No. of END (%)	No of pts. with pN+ (%)	Oral cavity/Oropharynx N (%)	Sinonasal N (%)	MSG* N (%)
Amit (2015)	457	226 (49.5)	38 (17.3)	25 (21.5)	4 (16.7)	9 (10.6)
Cordesmeier (2018)	59	34 (57.6)	7 (20.6) [†]			
Qian (2019)	1504 [‡]	1190 (79.1)				104 (8.7)
Xiao (2019)	2807 [§]	636 (22.7)	85 (13.4)			
Atallah (2020)	322	149 (46.3) [¶]	7 (4.7)	4 (57.1)	1 (14.3)	2 (28.6)

* major salivary glands

[†] 57.1% (4/7) of all occult neck metastases occurred in oral cavity primaries

[‡] 314 patients had no lymph nodes sampled

[§] 1422 patients (50.7%) had major salivary gland primaries

[¶] after propensity score matching 96 patients were undergoing END submitted to survival analysis

Table 2. Patient's demographic and clinical characteristics.

	No END	END
Age, mean (y)	63.2	61
Female (%)	61.9	58.4
MSG* (%)	52.5	81.8
T1/T2 stage (%)	65.4	64.5
Adjuvant radiotherapy (%)	68.6	74.3

* major salivary glands