Abstract: The purpose of this study was to evaluate the role of neck lymph node (ND) in the combined dissection modality therapy for locoregionally advanced head and neck cancer.

Methods: We identified patients with N2–N3 head and neck cancers who were enrolled in three consecutive multicenter phase II studies of concurrent chemoradiotherapy utilizing 5-fluorouracil and hydroxyurea on an alternate-week schedule with radiotherapy twice daily plus either cisplatin (C-FHX) or paclitaxel (T-FHX). Patients with unknown primary tumors, nasopharyngeal or paranasal sinus primaries, nonsquamous histology, progression or death during therapy, or incomplete therapy were excluded.

Results. A total of 131 patients were analyzed. Seventy-nine percent had N2 stage. ND was performed in 92 patients (70%), either prior to enrollment (n = 31) or after chemoradiotherapy (n = 61). With a median follow-up of 4.6 years, the 5-year locoregional and neck progression-free survival (PFS) rates were higher in patients with ND versus patients without ND: 88% versus 74% (p = .02) and 99% versus 82% (p = .0007), respectively; there was also a trend toward improved overall survival (OS) with ND, but PFS and distant PFS were comparable. In the subset of patients with N3 disease, ND was associated not only with better locoregional control but also with improved distant PFS. However, in patients with clinical complete response (n = 92), no significant differences in PFS (68% vs 75% at 5 years, p = .53) or any other survival parameters with or without ND were observed.

Conclusions. ND improves neck control and is required for patients with clinically residual disease or N3 neck cancer but has no significant impact on the outcome of patients with N2 stage disease who are rendered clinically disease-free with intensive concurrent chemoradiotherapy.

Keywords: neck dissection; chemotherapy; radiotherapy; head and neck cancer; squamous cell carcinoma

Neck lymph nodes are commonly involved by head and neck cancer. The traditional management of the neck in cases in which surgery is the primary
therapy usually involves a modified neck dissection that is followed by radiation therapy. In recent years, concurrent chemoradiotherapy has become a widely accepted treatment for selected patients with locoregionally advanced head and neck cancer. High rates of locoregional control have been reported with the use of intensive chemoradiotherapy regimens that allow for organ preservation and limit the role of salvage surgery for the primary tumor. However, the optimal management of the neck in the multimodal therapy of locoregionally advanced head and neck cancer that includes concomitant chemoradiotherapy has been controversial. Neck lymph node dissection (ND) has been utilized as a part of organ-preservation strategies in an elective manner, even after a complete response has been achieved, in order to optimize regional control. Some authors recommend elective ND after radiotherapy or chemoradiotherapy for patients with N2–N3 or N3 stage, regardless of response. Other investigators have favored elective ND only for patients with less than a complete response in the neck after induction chemotherapy, radiation therapy alone, or sequential chemoradiotherapy. We previously reported that selective ND is associated with a relatively low complication rate when performed 4 to 12 weeks after concurrent chemoradiotherapy and that 35% of ND dissection specimens after chemoradiotherapy harbor microscopic residual tumor. However, the impact of ND on the long-term outcome of patients with locoregionally advanced head and neck cancer undergoing concurrent chemoradiotherapy has not been adequately evaluated. Therefore, we analyzed three mature consecutive phase II clinical trials of concurrent chemoradiotherapy in order to determine the impact of ND on locoregional and distant-progression–free survival and the overall survival of patients with locoregionally advanced head and neck cancer with N2 or N3 stage treated on aggressive chemoradiotherapy programs.

**PATIENTS AND METHODS**

We performed a retrospective analysis of three consecutive multicenter phase II studies conducted at three academic institutions in Chicago, ie, University of Chicago, Northwestern University, and University of Illinois, and affiliated hospitals. The study protocols were approved by the individual Institutional Review Boards, and subjects signed informed consent. From September 1993 to March 1999, 230 patients with locoregionally advanced head and neck cancer, of whom 167 (73%) had N2 or N3 disease, were enrolled in these studies. The chemoradiotherapy regimens included concurrent 5-fluorouracil (5-FU) and hydroxyurea on an alternate-week schedule (1 week on, 1 week off) and twice daily radiation therapy, with either cisplatin (C-FHX regimen) or paclitaxel (T-FHX regimen) (see Table 1). Results from these studies and detailed methodology have been previously reported. ND

### Table 1. Phase II chemoradiotherapy trials at the Chicago Network.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total no. of patients treated on protocol</th>
<th>No. of patients included in analysis</th>
<th>Years</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C–FHX⁴</td>
<td>76</td>
<td>46</td>
<td>1993–1996</td>
<td>3</td>
</tr>
<tr>
<td>T(120 h)–FHX⁵</td>
<td>64</td>
<td>37</td>
<td>1995–1997</td>
<td>15</td>
</tr>
<tr>
<td>T(1 h)–FHX⁶</td>
<td>90</td>
<td>48</td>
<td>1997–1999</td>
<td>16</td>
</tr>
</tbody>
</table>

⁴C–FHX, cisplatin, 5-FU, hydroxyurea, radiation. Cisplatin 100 mg/m² on cycles 1, 3, and 5, 5-FU 800 mg/m²/d x 5 days, hydroxyurea 1000 mg orally BID x 11 doses, BID radiation 150 cGy per fraction/300 cGy daily, 1 week on, 1 week off to 65–75 Gy; cycles are repeated every 14 days until the completion of radiotherapy. Abbreviations: BID, twice daily; d, day.

⁵T(120 h)–FHX, paclitaxel as a 120-h infusion, 5-FU, hydroxyurea, radiation. Paclitaxel 100 mg/m² as a CI for 5 days (ie, 120 h), 5-FU 600 mg/m²/d x 5 days, hydroxyurea 500 mg orally BID x 11 doses, BID radiation 150 cGy per fraction/300 cGy daily, 1 week on, 1 week off to 65–75 Gy; cycles are repeated every 14 days until the completion of radiotherapy. Abbreviation: CI, continuous infusion.

⁶T(1 h)–FHX, paclitaxel as a 1-h infusion, 5-FU, hydroxyurea, radiation. Paclitaxel 100 mg/m² in 1 h on day 1, 5-FU 600 mg/m²/d x 5 days, hydroxyurea 500 mg orally BID x 11 doses, BID radiation 150 cGy per fraction/300 cGy daily, 1 week on, 1 week off to 65–75 Gy; cycles are repeated every 14 days until the completion of radiotherapy.

### Table 2. Patient exclusion criteria.

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal primary</td>
<td>3</td>
</tr>
<tr>
<td>Paranasal sinus primary</td>
<td>1</td>
</tr>
<tr>
<td>Parotid primary</td>
<td>1</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>11</td>
</tr>
<tr>
<td>Nonsquamous histology</td>
<td>1</td>
</tr>
<tr>
<td>Early death</td>
<td>8</td>
</tr>
<tr>
<td>Early progression</td>
<td>8</td>
</tr>
<tr>
<td>Declined treatment</td>
<td>2</td>
</tr>
<tr>
<td>Incomplete treatment due to complications</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>36</strong></td>
</tr>
</tbody>
</table>
prior to entering protocol therapy was allowed. Elective ND for N2–N3 stage of disease was a recommended but not mandatory part of these multimodality programs. Post-chemoradiotherapy selective ND procedures were usually performed within 4 to 12 weeks after completion of chemoradiotherapy. In order to examine a more homogeneous population and to eliminate potential biases in the selection of patients for ND, we excluded patients with unknown primary tumors, nasopharyngeal, paranasal sinus, or salivary gland primaries, nonsquamous histology, progression during therapy, toxic deaths, or incomplete therapy for any reason (see Table 2). After excluding 36 patients for one or more of the above reasons, 131 patients were analyzed. Clinical and radiographic complete response was defined as complete disappearance of detectable disease as evident by clinical examination, including endoscopy, and imaging studies (CT or MRI), respectively. Partial response was defined as reduction by at least 50% of the products of the longest perpendicular diameters of measurable tumor lesions. Overall survival was calculated from the date of treatment initiation to the date of death or last follow-up. Progression-free survival was calculated from the time of treatment initiation to the time of disease recurrence, death, or last follow-up. Survival curves were constructed using the Kaplan-Meier method and compared using log rank. Univariate analysis was performed using chi-square or Fisher’s exact test (two-sided) and multivariate analysis was performed for actuarial outcomes using a Cox regression model. Statistical analysis was performed using the SPSS version 10 (SPSS Inc., Chicago, IL).

RESULTS

A total of 131 patients fulfilled the inclusion criteria. The mean age was 55 years (range, 18–94).

| Table 3. Patient characteristics and treatment (n = 131). |
|-------------------------------|-----------------|
| Mean age, years (range)       | 55 (18–74)      |
| Sex, no. patients (%)         |                  |
| Male                          | 99 (76)         |
| Female                        | 32 (24)         |
| Primary site, no. patients (%)|                  |
| Oropharynx                    | 70 (53)         |
| Hypopharynx                   | 20 (15)         |
| Oral cavity                   | 21 (16)         |
| Larynx                        | 20 (15)         |
| Protocol, no. patients (%)    |                  |
| 1. C–FHX                      | 46 (35)         |
| 2. T(120 h)–FHX               | 37 (28)         |
| 3. T(1 h)–FHX                 | 48 (37)         |
| Radiation dose, Gy            |                  |
| Mean (range)                  | 74 (59–76)      |
| Timing of neck dissection, no. patients (%) |
| Before to chemoradiotherapy   | 31 (24)         |
| After chemoradiotherapy       | 61 (47)         |
| None                          | 39 (30)         |

<table>
<thead>
<tr>
<th>Table 4. TNM stage distribution (no. patients).</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2a</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>%</td>
</tr>
</tbody>
</table>

FIGURE 1. Kaplan-Meier estimates of overall survival in all patients (A, N = 131) and patients with clinical complete response (B, n = 92); (- - -) with neck dissection; (—) without neck dissection.
Patient characteristics are displayed in Table 3. Ninety-nine patients (76%) were men, and 32 (24%) were women. Primary sites included the oropharynx [70 (53%)], hypopharynx [20 (15%)], oral cavity [21 (16%)], and larynx [20 (15%)]. Stage distribution is displayed in Table 4. ND was performed in 92 patients (70%), either prior to enrollment (31 patients) or after chemoradiotherapy (61 patients). Twenty-two bilateral and 70 unilateral NDs were performed. Post-chemoradiotherapy ND was performed at a median time of 17 weeks (range, 13–28 weeks) after treatment initiation, whereas prechemoradiotherapy ND was performed at a median of 32 days prior to treatment initiation. At the time of post-chemoradiotherapy neck dissection, only two patients underwent salvage surgery for an active primary. There were differences in institutional preferences regarding the use or not of elective ND. Seventeen (39%) of 44 patients who were treated at one of the institutions had ND versus 50/54 (93%) and 14/18 (78%) of the patients treated at the two other major institutions (p < .05). On univariate analysis, no other parameter that may have influenced the decision for performing ND was found to be of statistical significance.

### Table 5. Univariate analysis of prognostic factors for progression-free survival (PFS) and locoregional progression-free survival (LPFS).

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>No. patients with recurrence at any site (locoregional)</th>
<th>Actuarial 5-year LPFS (%)</th>
<th>p value</th>
<th>Actuarial 5-year PFS (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>37</td>
<td>12 (7)</td>
<td>75</td>
<td>0.13</td>
<td>62</td>
<td>0.22</td>
</tr>
<tr>
<td>&gt;50</td>
<td>94</td>
<td>25 (10)</td>
<td>88</td>
<td>0.18</td>
<td>75</td>
<td>0.14</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>99</td>
<td>30 (15)</td>
<td>82</td>
<td>0.76</td>
<td>68</td>
<td>0.14</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>5 (2)</td>
<td>91</td>
<td>0.76</td>
<td>81</td>
<td>0.14</td>
</tr>
<tr>
<td>Primary Site</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70</td>
<td>13 (8)</td>
<td>88</td>
<td>0.02</td>
<td>80</td>
<td>0.54</td>
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<tr>
<td>Hypopharynx</td>
<td>20</td>
<td>7 (2)</td>
<td>88</td>
<td>0.02</td>
<td>64</td>
<td>0.54</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>21</td>
<td>9 (4)</td>
<td>73</td>
<td>0.02</td>
<td>53</td>
<td>0.54</td>
</tr>
<tr>
<td>Larynx</td>
<td>20</td>
<td>6 (3)</td>
<td>81</td>
<td>0.02</td>
<td>67</td>
<td>0.54</td>
</tr>
<tr>
<td>T classification</td>
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<tr>
<td>T1</td>
<td>13</td>
<td>2 (1)</td>
<td>92</td>
<td>0.66</td>
<td>85</td>
<td>0.81</td>
</tr>
<tr>
<td>T2</td>
<td>25</td>
<td>7 (1)</td>
<td>96</td>
<td>0.66</td>
<td>72</td>
<td>0.81</td>
</tr>
<tr>
<td>T3</td>
<td>34</td>
<td>7 (0)</td>
<td>100</td>
<td>0.66</td>
<td>77</td>
<td>0.81</td>
</tr>
<tr>
<td>T4</td>
<td>59</td>
<td>19 (15)</td>
<td>70</td>
<td>0.66</td>
<td>64</td>
<td>0.81</td>
</tr>
<tr>
<td>N classification</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N2a</td>
<td>8</td>
<td>2 (2)</td>
<td>69</td>
<td>0.43</td>
<td>69</td>
<td>0.40</td>
</tr>
<tr>
<td>N2b</td>
<td>65</td>
<td>15 (7)</td>
<td>87</td>
<td>0.43</td>
<td>75</td>
<td>0.40</td>
</tr>
<tr>
<td>N2c</td>
<td>31</td>
<td>10 (4)</td>
<td>84</td>
<td>0.43</td>
<td>66</td>
<td>0.40</td>
</tr>
<tr>
<td>N3</td>
<td>27</td>
<td>8 (4)</td>
<td>84</td>
<td>0.43</td>
<td>69</td>
<td>0.40</td>
</tr>
<tr>
<td>Protocol therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C―FHX</td>
<td>46</td>
<td>9 (4)</td>
<td>89</td>
<td>0.43</td>
<td>74</td>
<td>0.40</td>
</tr>
<tr>
<td>T(120 h)―FHX</td>
<td>37</td>
<td>10 (7)</td>
<td>78</td>
<td>0.43</td>
<td>70</td>
<td>0.40</td>
</tr>
<tr>
<td>T(1 h)―FHX</td>
<td>48</td>
<td>16 (6)</td>
<td>87</td>
<td>0.43</td>
<td>67</td>
<td>0.40</td>
</tr>
<tr>
<td>Neck dissection</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before CRT</td>
<td>31</td>
<td>7 (3)</td>
<td>88</td>
<td>0.43</td>
<td>76</td>
<td>0.57</td>
</tr>
<tr>
<td>After CRT</td>
<td>61</td>
<td>15 (5)</td>
<td>90</td>
<td>0.43</td>
<td>74</td>
<td>0.57</td>
</tr>
<tr>
<td>None</td>
<td>39</td>
<td>13 (9)</td>
<td>74</td>
<td>0.43</td>
<td>64</td>
<td>0.57</td>
</tr>
<tr>
<td>Clinical response (n = 116)*</td>
<td></td>
<td></td>
<td></td>
<td>0.13</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>92</td>
<td>25 (11)</td>
<td>86</td>
<td>0.13</td>
<td>71</td>
<td>0.50</td>
</tr>
<tr>
<td>Partial</td>
<td>24</td>
<td>8 (6)</td>
<td>73</td>
<td>0.13</td>
<td>65</td>
<td>0.50</td>
</tr>
<tr>
<td>Radiographic response (n = 115)*</td>
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<td></td>
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<td>0.50</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>72</td>
<td>20 (8)</td>
<td>86</td>
<td>0.50</td>
<td>69</td>
<td>0.89</td>
</tr>
<tr>
<td>Partial</td>
<td>43</td>
<td>11 (7)</td>
<td>82</td>
<td>0.50</td>
<td>73</td>
<td>0.89</td>
</tr>
<tr>
<td>Pathology at ND after CRT (n = 61)</td>
<td></td>
<td></td>
<td></td>
<td>0.55</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
<td>7 (2)</td>
<td>89</td>
<td>0.55</td>
<td>62</td>
<td>0.11</td>
</tr>
<tr>
<td>Negative</td>
<td>42</td>
<td>8 (3)</td>
<td>91</td>
<td>0.55</td>
<td>80</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Abbreviations: CRT, chemoradiotherapy; C―FHX, cisplatin, 5-FU, hydroxyurea, radiation; T―FHX, paclitaxel, 5-FU, hydroxyurea, radiation; ND, neck dissection.

*The rest of the patients were nonevaluable for response.
Relapse and Survival Outcomes. The median follow-up for surviving patients was 4.6 years (range, 2.8–7.9). Thirty-five (27%) of a total of 131 patients have had recurrences: 13 in locoregional sites only, 18 in distant sites only, and four both distantly and locoregionally. Only seven patients had relapses in the neck lymph nodes. The actuarial 5-year progression-free survival (PFS) rate was 74% with ND versus 64% without ND ($p = .29$), and the 5-year overall survival (OS) rate was 58% versus 41% ($p = .07$) (see Figures 1–3).

Locoregional PFS (LPFS) was higher in patients undergoing ND: 88% versus 74% at 5 years ($p = .02$), but distant PFS (DPFS) was comparable: 84% versus 77% ($p = .86$).

Neck Control. Neck failure was rare with or without ND. However, the addition of ND to chemoradiotherapy resulted in only one neck failure in 92 patients (actuarial neck PFS 99%) versus six neck failures in 39 patients (actuarial neck PFS 82%) not undergoing ND ($p = .0007$) (Figure 4A). The addition of ND was of lesser importance for neck control in patients with a clinical complete response (CR) ($n = 92$): one of 62 patients (actuarial neck PFS 98%) had recurrence in the neck with ND and two of 30 patients (actuarial neck PFS 92%) had recurrence in the neck without ND ($p = .21$) (Figure 4B). Of the two patients with CR who did not undergo ND and failed in the neck, one had N2c and one had N3 stage; the patient with N3 neck disease had distant metastasis as well. Thus, only one of 30 patients with clinical CR who did not have ND developed an isolated neck recurrence.

Response and N Stage as Predictors of Outcome. Clinical response as well as pathologic complete

![FIGURE 2. Kaplan-Meier estimates of progression-free survival in all patients (A, $N = 131$) and patients with clinical complete response (B, $n = 92$); (- - -) with neck dissection; (—) without neck dissection.](image1)

![FIGURE 3. Kaplan–Meier estimates of locoregional progression-free survival in all patients (A, $N = 131$) and patients with clinical complete response (B, $n = 92$); (- - -) with dissection; (—) without neck dissection.](image2)
response after chemoradiotherapy were border-
line predictive of LPFS, but the differences did
not reach statistical significance (see univariate
analysis in Table 5). When radiographic re-
response was used to analyze differences in survi-
val between patients with ND versus without ND,
the magnitude of differences was smaller than
when clinical response was used. Finally, the
timing of ND, ie, before or after chemoradiothe-
dapy, did not influence any survival parameter.

In 92 patients who achieved a clinical CR
after chemoradiotherapy, ND did not improve
any survival outcome (see Figures 1B, 2B, 3B,
and 4B and Table 6). At 5 years, LPFS was 85%
with ND versus 85% without ND ($p = .84$), PFS
was 68% versus 75% ($p = .53$), and OS was 53%
versus 49% ($p = .95$). Disease stage and other
parameters were evenly distributed between
patients who did or did not undergo ND (see
Table 7). In a total of 24 patients with partial
response (PR) after chemoradiotherapy (patients
with N2 and N3 stages combined), six of 8
patients who did not undergo ND relapsed
versus two of 16 patients who underwent ND
($p = .005$). Eight patients did not undergo ND
despite having a clinical PR for the following
reasons: patient refusal ($n = 1$), surgeon’s
decision ($n = 3$), radiographic CR ($n = 1$),

![Neck Progression-free Survival](image)

**FIGURE 4.** Kaplan-Meier estimates of neck progression-free survival in all patients (A, $N = 131$) and patients with clinical complete
response (B, $n = 92$); (– —) with dissection; (—) without neck dissection.

<table>
<thead>
<tr>
<th>Patient group (no.)</th>
<th>OS (%)</th>
<th>PFS (%)</th>
<th>LPFS (%)</th>
<th>LNPFS (%)</th>
<th>DPFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cCR, no ND (30)</td>
<td>49% (14)</td>
<td>75% (7)</td>
<td>85% (4)</td>
<td>92% (2)</td>
<td>81% (5)</td>
</tr>
<tr>
<td>cPR, yes ND (62)</td>
<td>53% (31)</td>
<td>68% (18)</td>
<td>85% (7)</td>
<td>98% (1)</td>
<td>81% (11)</td>
</tr>
<tr>
<td>N2, no ND (7)</td>
<td>29% (5)</td>
<td>36% (4)</td>
<td>54% (3)</td>
<td>86% (1)</td>
<td>36% (4)</td>
</tr>
<tr>
<td>N2, yes ND (72)</td>
<td>55% (9)</td>
<td>79% (4)</td>
<td>94% (1)</td>
<td>100% (0)</td>
<td>84% (3)</td>
</tr>
<tr>
<td>N2, no ND (32)</td>
<td>45% (18)</td>
<td>70% (9)</td>
<td>79% (6)</td>
<td>82% (5)</td>
<td>86% (4)</td>
</tr>
<tr>
<td>N2, yes ND (72)</td>
<td>59% (32)</td>
<td>72% (18)</td>
<td>87% (7)</td>
<td>98% (1)</td>
<td>84% (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient group (no.)</th>
<th>OS (%)</th>
<th>PFS (%)</th>
<th>LPFS (%)</th>
<th>LNPFS (%)</th>
<th>DPFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cCR, yes ND (62)</td>
<td>53% (31)</td>
<td>68% (18)</td>
<td>85% (7)</td>
<td>98% (1)</td>
<td>81% (11)</td>
</tr>
<tr>
<td>N3, no ND (7)</td>
<td>29% (5)</td>
<td>36% (4)</td>
<td>54% (3)</td>
<td>86% (1)</td>
<td>36% (4)</td>
</tr>
<tr>
<td>N3, yes ND (20)</td>
<td>55% (9)</td>
<td>79% (4)</td>
<td>94% (1)</td>
<td>100% (0)</td>
<td>84% (3)</td>
</tr>
<tr>
<td>N2, no ND (32)</td>
<td>45% (18)</td>
<td>70% (9)</td>
<td>79% (6)</td>
<td>82% (5)</td>
<td>86% (4)</td>
</tr>
<tr>
<td>N2, yes ND (72)</td>
<td>59% (32)</td>
<td>72% (18)</td>
<td>87% (7)</td>
<td>98% (1)</td>
<td>84% (11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient group (no.)</th>
<th>OS (%)</th>
<th>PFS (%)</th>
<th>LPFS (%)</th>
<th>LNPFS (%)</th>
<th>DPFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cPR, yes ND (16)</td>
<td>68% (5)</td>
<td>87% (2)</td>
<td>93% (1)</td>
<td>100% (0)</td>
<td>94% (1)</td>
</tr>
<tr>
<td>N3, no ND (7)</td>
<td>29% (5)</td>
<td>36% (4)</td>
<td>54% (3)</td>
<td>86% (1)</td>
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</tr>
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</tr>
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<td>45% (18)</td>
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<td>59% (32)</td>
<td>72% (18)</td>
<td>87% (7)</td>
<td>98% (1)</td>
<td>84% (11)</td>
</tr>
</tbody>
</table>

Abbreviations: ND, neck dissection; cCR, clinical complete response; cPR, clinical partial response; OS, overall survival; PFS, progression-free survival;
LPFS, locoregional progression-free survival; LNPFS, neck progression-free survival; DPFS, distant progression-free survival.

The number of patients who failed is in parentheses in each column.

*p values are for the comparison of patients undergoing ND versus patients not undergoing ND.
negative neck lymph node biopsy (n = 1), and unknown (n = 2).

In patients with N3 stage disease (n = 27), there was either a trend or a statistically significant difference in survival parameters in favor of patients who underwent ND versus patients who did not have ND (see Table 6). On the other hand, in 104 patients with N2 disease, neck control improved with ND but OS, PFS, LPFS, and DPFS were similar with or without ND (see Table 6). The distribution of patients with recurrences according to N stage and response to treatment is displayed in Table 8. Finally, there were no significant differences in outcome between patients with N2a, N2b, or N2c stages. In multivariate analysis using a Cox regression model, stage T4 and the performance of ND were independent predictors of neck and locoregional PFS.

Pathologic Response. Sixty-one patients underwent ND after completion of chemoradiotherapy and were evaluated for pathologic response. Of these 61 patients, 42 (69%) had negative and 19 (31%) had positive residual tumor pathology. There was discordance between clinical and pathologic response (see Figure 5): 27 (61%) of 44 patients with clinical CR had a pathologic CR, whereas a higher percentage of patients, 14 (87.5%) of 16, with a clinical PR had a pathologic CR (p = .07). Pathologic CR did not predict disease control. Three of 42 patients with no residual tumor on pathology had locoregional recurrences (actuarial LPFS 91%), one of these in the neck, whereas two of 19 patients with positive pathology had locoregional recurrences (actuarial LPFS 89%) (p = .55) but none in neck nodes. In a total of 44 patients who underwent post-chemoradiotherapy ND in the setting of a clinical CR, 6 of 17 patients with positive pathology had a relapse versus 7 of 27 for patients with negative pathology on ND (p = .52); in 16 patients with clinical PR after chemoradiotherapy, one of two patients with positive pathology had a relapse versus one of 14 patients with negative pathology (p = .24).

**DISCUSSION**

We evaluated the impact of ND on the outcome of patients with N2 or N3 squamous cell carcinoma of the head and neck undergoing intensive concurrent chemoradiotherapy on three consecutive

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**Table 7.** Univariate analysis of characteristics of patients with complete response according to ND status (n = 92); percentages in parentheses.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Without ND (n = 32)</th>
<th>With ND (n = 60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50</td>
<td>22 (73)</td>
<td>43 (69)</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;50</td>
<td>8 (27)</td>
<td>19 (31)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Male</td>
<td>23 (77)</td>
<td>44 (71)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (23)</td>
<td>18 (29)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>19 (63)</td>
<td>36 (58)</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>4 (13)</td>
<td>11 (18)</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>4 (13)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>3 (10)</td>
<td>10 (16)</td>
<td></td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>T1</td>
<td>1 (3)</td>
<td>6 (10)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>7 (23)</td>
<td>12 (19)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>9 (30)</td>
<td>14 (23)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>13 (43)</td>
<td>30 (48)</td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>N2a</td>
<td>2 (7)</td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td>N2b</td>
<td>6 (20)</td>
<td>14 (23)</td>
<td></td>
</tr>
<tr>
<td>N2c</td>
<td>13 (43)</td>
<td>31 (50)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>9 (30)</td>
<td>13 (21)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 8.** Relapse rate (any site) according to neck stage and overall clinical response.

<table>
<thead>
<tr>
<th>Neck dissection</th>
<th>No. of patients relapsed (%)</th>
<th>No. of patients relapsed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2 neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>48 14 (28)</td>
<td>24 4 (17)</td>
</tr>
<tr>
<td>PR</td>
<td>10 2 (20)</td>
<td>7 5 (71)*</td>
</tr>
<tr>
<td>NE</td>
<td>14 2 (14)</td>
<td>1 0 (0)</td>
</tr>
<tr>
<td>N3 neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>14 4 (25)</td>
<td>6 3 (50)</td>
</tr>
<tr>
<td>PR</td>
<td>6 0 (0)</td>
<td>1 1 (100)</td>
</tr>
</tbody>
</table>

*p < .05 compared with patients who underwent ND.
therapeutic protocols. Although this analysis is retrospective, prospective or randomized studies of ND will be extremely difficult to conduct. Previous studies either included patients treated with sequential chemoradiotherapy or had small sample sizes and/or did not analyze patterns of failure and long-term survival data.\textsuperscript{6,8,9,14,17} Our results indicate that ND improves neck control and is associated with better locoregional control and a trend toward improved OS. However, ND had no impact on DPFS or PFS. Subset analysis showed that the benefit from ND is restricted to patients with N3 disease and to patients who achieve less than a CR. In other words, the data presented suggest that ND can be safely omitted in patients with N2 neck who are clinically disease free at the completion of concurrent chemoradiotherapy. It should be noted that in our study, multiagent chemotherapy and hyperfractionated radiotherapy were administered with favorable locoregional control and the emergence of distant metastases as the predominant site of failure.\textsuperscript{18} It is likely that when less aggressive chemoradiotherapy programs are used, the contribution of ND in locoregional control becomes more important.

The value of postoperative radiation therapy in improving neck control has been established,\textsuperscript{19,20} whereas the addition of chemotherapy to postoperative radiation is under investigation.\textsuperscript{21} Concurrent chemoradiotherapy is increasingly utilized as primary therapy in order to achieve organ preservation and improve survival of patients with head and neck cancer. Conversely, neck surgery has in many cases assumed an adjunct role. In that context, our observations are important for defining the role of ND when patients are treated with definitive concurrent chemoradiotherapy.

A number of studies have reported on the role of ND either after definitive radiation, alternating chemoradiotherapy, or induction chemotherapy followed by radiation therapy.\textsuperscript{6,7,9,13,14,17,22} Similar to our findings, Sanguineti et al\textsuperscript{7} reported a 35% rate of pathologic positivity in elective ND specimens.\textsuperscript{22} Lavertu et al\textsuperscript{6} conducted a subset analysis of a randomized study that compared radiotherapy alone with radiotherapy and concurrent chemotherapy consisting of cisplatin and 5-fluorouracil. Of 35 N2–N3 patients who underwent ND, 12 (34%) had residual tumors. In 30 patients with clinical CR after radiation or chemoradiotherapy, none of 18 patients who underwent ND relapsed in the neck but three of 12 patients who did not undergo ND relapsed in the neck (p = .05); however, the disease-specific survival was not different. We have previously reported a 35% rate of pathologic positivity in elective ND specimens after aggressive chemoradiotherapy that was even higher (50%) in patients with N3 disease; no survival outcome analysis was conducted at that time, and single-institution data were reported.\textsuperscript{14} In accordance with our previous findings, we observed that 39% of patients with CR after chemoradiotherapy harbored residual tumors on elective ND specimens. Despite risk of pathologic residual disease, only seven (23%) of 30 patients with CR who did not have ND relapsed at any site and only two (7%) of 30 relapsed in the neck. To explain this observation, we hypothesize that, in the majority of cases, microscopic residual disease represents nonviable tumors. Corroborating our hypothesis, Strasser et al\textsuperscript{23} have reported proliferating cancer...
cells as determined by positivity for Ki-67 in only three of 17 post-radiotherapy ND specimens, whereas 11 of these 17 specimens contained cancer by microscopic examination.

Selective ND can be generally safely performed after chemoradiotherapy within a window period of 4 to 12 weeks; however, significant complications may occur in 26% of patients. Therefore, even though ND does not sacrifice an organ, the avoidance of ND may potentially spare patients additional morbidity. Noninvasive methods that may further delineate the subset of patients who will benefit from ND, such as positron emission tomography scanning, warrant investigation. In conclusion, this retrospective analysis identified N3 disease and less-than-complete response as risk factors that necessitate the addition of ND for optimal disease control. However, ND may be safely omitted in patients with N2 stage who achieve a clinical CR after intensive chemoradiotherapy.

REFERENCES