Nasolacrimal duct obstruction following radioactive iodine 131 therapy in differentiated thyroid cancers: review of 19 cases

Khalid Hussain Al-Qahtani1
Mushabbab Al Asiri2
Mutahir A Tunio3
Naji J Aljohani3
Yasser Bayoumi4
Iqbal Munir5
Ayman AlAyoubi6

1Department of Otolaryngology – Head and Neck Surgery, College of Medicine, Advanced Head and Neck Oncology, King Saud University.
2Radiation Oncology, Comprehensive Cancer Center, King Fahad Medical City.
3Endocrinology and Thyroid Oncology, King Fahad Medical City, Riyadh, Saudi Arabia.
4Radiation Oncology, NCI, Cairo University, Cairo, Egypt.
5Nuclear Medicine, Sulaiman Al-Habib Hospital.
6Clinical Ophthalmology, King Fahad Medical City, Riyadh, Saudi Arabia

Background: Radioactive iodine 131 (131I) therapy has long been used in the treatment of differentiated thyroid cancers (DTC). While salivary and lacrimal glandular complications secondary to 131I therapy are well documented, there is little in the literature addressing nasolacrimal duct obstruction (NLDO). We aimed to evaluate the frequency of 131I therapy-acquired NLDO, its correlation to 131I therapy doses, and the surgical treatment outcome of this rare side effect.

Methods: From 2000–2012, a retrospective review of 864 among 1,192 patients with confirmed DTC who were treated with 131I therapy was performed to examine the frequency of NLDO, its causative factors, as well as imaging, surgical intervention, and outcomes.

Results: Nineteen (2.2%) patients were identified with NLDO. The mean age was 51.9±10.5 years (range: 39–72 years). Fifteen (78.9%) were female and four were male (21.1%). The mean individual 131I doses were 311.1±169.3 millicurie (mCi) (range: 150–600 mCi). The mean duration between the date of 131I therapy and the occurrence of NLDO was 11.6±4.1 months (range: 6.5–20). Fourteen (73.7%) patients had bilateral epiphora. Computed tomography dacryography allowed for the detection of all NLDO. Eighteen (94.7%) patients underwent dacryocystorhinostomy. Complete recovery was obtained in 14 (73.7%) patients. Age >45 years and 131I therapy doses >150 mCi were significantly correlated with NLDO (P=0.02 and P=0.03, respectively).

Conclusion: NLDO is an underestimated complication of 131I therapy in DTC patients. Clinicians should be aware of this rare complication for prompt intervention.

Keywords: nasolacrimal duct obstruction, radioactive iodine 131 therapy, differentiated thyroid cancers

Introduction

The use of post-thyroidectomy adjuvant radioactive iodine 131 (131I) therapy is associated with dramatic decreases in locoregional recurrences, distant metastasis, and disease-related mortality in patients with differentiated thyroid carcinomas (DTC). Although generally well tolerated, 131I therapy is associated with substantial, albeit rare, side effects. While gastrointestinal problems, salivary and lacrimal gland complications, gonadal dysfunction, and second malignancies are well documented side effects of 131I therapy, there is scant literature addressing nasolacrimal duct obstruction (NLDO).2,3 Different studies have mentioned that the incidence of NLDO was around 3% among DTC patients treated with 131I therapy. The common presentation is an excessive overflow of tears (epiphora). Other signs and symptoms are the medial canthus mass, recurrent conjunctivitis, or infection (dacyrocystitis).4

In the Kingdom of Saudi Arabia, DTC has become the second most common malignancy, behind only breast cancer, accounting for more than 10% of all cancers among...
women. The majority of these patients require adjuvant 
$I$ therapy at some point; only a small proportion of these 
patients can be at risk of $I$ therapy-acquired NLDO, which 
was the aim of our study. We also aimed to determine the 
correlation between NLDO and $I$ therapy along with other 
clinical and treatment parameters in DTC patients receiving 
$I$ therapy in our population.

**Methods**

After formal approval from the institutional ethics commit-
tee, the medical records of 864 patients, among a total of 
1,192 patients, with confirmed DTC who were treated with 
$I$ therapy in two major tertiary care hospitals during the 
period from July 2000–December 2012 were reviewed using 
a computer-based institutional database system. Patients with 
NLDO were retrieved in the following manner:

- Demographic information (age at diagnosis and sex), 
  as well as data regarding symptomatology, clinical 
  procedures (anterior rhinoscopy and Jones fluorescein 
  dye test), and $I$ therapy doses in millicurie (mCi) were 
  collected.
- Information on the different diagnostic imaging modalities 
  used, including dacryoscintigraphy, computed tomogra-
  phy (CT) dacryography of the neck, and fluordeoxyglu-
  cose positron emission tomography, was collected.
- Data regarding the surgical intervention used, including 
  balloon dilation, stenting, dacryocystorhinostomy (DCR), 
  type of DCR (external or endoscopic endonasal), symp-
  toms relief, and duration of relief were also recorded.
- Any discrepancies in data acquisition were resolved by 
  directly questioning the patients and treating physicians 
  (ear, nose, and throat, oncology, ophthalmology, and 
  nuclear medicine).
- However, no attempt to systematize other associated 
  sinonasal problems (potential confounders) of the patients 
  was performed.

**Statistical analysis**

The primary endpoint was the frequency of NLDO. All 
descriptive data were reported as the mean $\pm$ standard 
deviation, and percentages. The secondary endpoint was the 
correlation of NLDO with $I$ therapy (as tested by Pearson’s 
correlation coefficients). Efforts were made to minimize 
the effects of potential confounders, which were controlled 
using multivariate analysis. Statistical analyses were per-
formed using the computer program SPSS version 16.0. The 
Kaplan–Meier method was used to predict the cumulative 
risk of NLDO in our series.

**Results**

Among the 864 DTC patients who were treated with $I$ ther-
apy, 19 (2.2%) were identified with NLDO (Table 1). No event 
of NLDO was seen in any patient who was untreated with $I$ 
therapy or was treated with $I$ therapy doses below 150 mCi. 
The mean age of the study population was 51.9 $\pm$ 10.5 years 
(range: 39–72 years), and our population consisted of 
15 females (78.9%) and four males (21.1%), with a female-
to-male ratio of 3.7:1. The mean individual $I$ dose was 
311.1 $\pm$ 169.3 mCi (range: 150–600 mCi). The mean duration 
between the date of $I$ therapy and the occurrence of apparent 
NLDO was 11.6 $\pm$ 4.1 months (range: 6.5–20 months).

Fourteen (73.7%) patients had bilateral epiphora. Dacryo-
scintigraphy allowed for the detection of 16 NLDO with a 
sensitivity of 84.2% (95% confidence interval [CI]: 60.4–96.4) 
and a specificity of 99.6% (95% CI: 98.9–99.9), while CT dacryo-
graphy detected all cases of NLDO with a sensitivity of 100% 
(95% CI: 82.2–100) and a specificity of 100% (95% CI: 82.2–100).

DCR was performed in 32 completely stenosed naso-
lacrimal ducts of 18 (94.7%) patients – either bilaterally 
(63.2%) or unilaterally (26.3%). Three patients (15.8%) 
had endoscopic endonasal DCR. Observation was planned 
for one patient; but the patient had partial relief and was 
considered for DCR. Among the DCR patients, complete 
recovery was obtained in 14 (73.7%) patients, and partial 
relief was obtained in three (15.8%) patients. The success 
rates of external DCR and endoscopic endonasal DCR were 
85.7% and 66.7%, respectively.

A significant correlation between NLDO and $I$ therapy 
doses above 150 mCi was seen ($R$=0.92; $R^2$=0.86; $P$=0.03). Multivariate analysis showed that $I$ therapy doses above 
150 mCi and an age $>45$ years were important prognostic-
ators (Figure 1).

**Discussion**

Acquired NLDO secondary to $I$ therapy is an extremely 
rare complication in patients with DTC. In our cohort, the 
frequency of NLDO of 2.2% is consistent with other reported 
results (Table 2). The incidence rate of NLDO in the 
general population is lacking, despite a detailed medical lit-
erature search. In the majority of cases, the diagnosis is made 
upon the basis of spontaneous reporting of epiphora by the 
patients. This diagnostic delay leads to complete stenosis 
of the nasolacrimal ducts, and thus renders these patients 
to aggressive treatment. In the clinical setting, the Jones 
fluorescein dye test is of significant value in NLDO patients.

One Australian study has demonstrated that a negative
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/sex</th>
<th>Diagnosis</th>
<th>$^{131}$I dose (mCi)</th>
<th>Symptoms</th>
<th>Onset from last $^{131}$I treatment (months)</th>
<th>DSG</th>
<th>CT dacryography</th>
<th>Treatment</th>
<th>Symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49/F</td>
<td>PTC T3N1M0</td>
<td>300</td>
<td>Bilateral epiphora</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>2</td>
<td>41/F</td>
<td>PTC T3N1M1</td>
<td>600</td>
<td>Right eye epiphora</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>Observation</td>
<td>Partial</td>
</tr>
<tr>
<td>3</td>
<td>65/F</td>
<td>FTC T3N1M1</td>
<td>400</td>
<td>Bilateral epiphora</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>4</td>
<td>53/F</td>
<td>PTC T4N1M0</td>
<td>150</td>
<td>Right eye epiphora</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>5</td>
<td>69/F</td>
<td>FTC T2N0M1</td>
<td>450</td>
<td>Bilateral epiphora</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>6</td>
<td>47/F</td>
<td>PTC T4N0M0</td>
<td>150</td>
<td>Left eye epiphora</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>7</td>
<td>51/F</td>
<td>FTC T3N1M1</td>
<td>550</td>
<td>Bilateral epiphora</td>
<td>20</td>
<td>+</td>
<td>+</td>
<td>EE-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>8</td>
<td>39/F</td>
<td>PTC T2N1M0</td>
<td>150</td>
<td>Bilateral epiphora</td>
<td>6.5</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>9</td>
<td>47/M</td>
<td>PTC T3N1M0</td>
<td>300</td>
<td>Bilateral epiphora</td>
<td>12.5</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>10</td>
<td>72/F</td>
<td>PTC T3N1M0</td>
<td>300</td>
<td>Right eye dacryocystitis</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>11</td>
<td>42/F</td>
<td>PTC T3N1M1</td>
<td>550</td>
<td>Bilateral epiphora</td>
<td>15</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Partial</td>
</tr>
<tr>
<td>12</td>
<td>42/M</td>
<td>PTC T2N1M0</td>
<td>150</td>
<td>Left eye epiphora</td>
<td>7.3</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>13</td>
<td>58/F</td>
<td>PTC T2N1M1</td>
<td>210</td>
<td>Bilateral epiphora</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>14</td>
<td>45/M</td>
<td>PTC T3N1M1</td>
<td>350</td>
<td>Bilateral epiphora</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>15</td>
<td>46/F</td>
<td>PTC T2N1M0</td>
<td>300</td>
<td>Bilateral epiphora</td>
<td>9</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Partial</td>
</tr>
<tr>
<td>16</td>
<td>66/F</td>
<td>PTC T2N1M0</td>
<td>300</td>
<td>Bilateral epiphora</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>EE-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>17</td>
<td>39/F</td>
<td>PTC T3N1M0</td>
<td>200</td>
<td>Bilateral epiphora</td>
<td>6.5</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
<tr>
<td>18</td>
<td>56/M</td>
<td>PTC T2N1M1</td>
<td>600</td>
<td>Bilateral epiphora</td>
<td>19</td>
<td>+</td>
<td>+</td>
<td>Left eye observation</td>
<td>Complete</td>
</tr>
<tr>
<td>19</td>
<td>60/F</td>
<td>PTC T4N0M1</td>
<td>600</td>
<td>Bilateral epiphora</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>E-DCR</td>
<td>Complete</td>
</tr>
</tbody>
</table>

**Abbreviations:** $^{131}$I, radioactive iodine; mCi, millicurie; DSG, dacryoscintigraphy; CT, computed tomography; F, female; PTC, papillary thyroid carcinoma; E-DCR, external dacryocystorhinostomy; FTC, follicular thyroid carcinoma; EE-DCR, endoscopic endonasal dacryocystorhinostomy; M, male.
single-drop Jones fluorescein dye test is also predictive of symptomatic improvement after DCR in patients with NLDO.11

The postulated mechanism for 131I therapy-acquired NLDO is the direct uptake of 131I in the nasolacrimal duct membrane epithelial cells via the sodium (Na+)/iodide (I) symporter (NIS) leading to radiation-induced cell damage (inflammation and fibrosis/stenosis).9 The NIS is a membrane glycoprotein that mediates 131I uptake in the thyroid gland and several other extrathyroid tissues (salivary glands, lacrimal glands, and ciliary body of the eye).12 Recently, Morgenstern et al13 have reported the overexpression of NIS in the nasolacrimal ducts using reverse transcriptase polymerase chain reaction and immunohistochemical analyses. In addition to the presence of sinonasal disease at the time of 131I therapy, the treatment may theoretically further decrease the flow in the nasolacrimal ducts and thus increase the exposure to 131I, which is secreted through the lacrimal system.3

The diagnosis of 131I therapy-acquired NLDO is challenging. Other possible causes (allergic or viral conjunctivitis, keratoconjunctivitis sicca, trichiasis, canalicularitis, iritis, and functional causes of excessive tears) should be ruled out to reach a definitive diagnosis of 131I therapy-acquired NLDO.14 131I therapy-acquired NLDO is defined as: 1) the presence of NLDO in 131I therapy-treated patients; 2) an 131I dose–NLDO relationship; 3) immediate onset of symptoms after 131I therapy; and 4) the bilateral nature of NLDO in most of cases. CT dacryography using diluted contrast medium was found to be an easy and highly sensitive tool to evaluate NLDO in our cohort, which endorsed the findings of Garicier et al.15

Patients with incomplete NLDO have an excellent outlook with the use of balloon dilation and stenting, as complete recovery of symptoms is observed in 100% of cases.3 Although the literature supports the hypothesis of complete symptom recovery with observation alone, in a few cases of incomplete NLDO, we did not find that observation was a feasible option. The reason for this can be explained by the fact that NLDO is possibly a chronic radiation-induced injury that progresses over a period of time.16 The DCR success rate of 78.9% in our cohort is consistent with the findings of Fonseca et al.6 However, the endoscopic endonasal DCR success rate of 60% is much inferior to that reported in the literature, which warrants more personnel training in this area in our region.17

Because NLDO impairs the quality of life of a patient significantly, prevention of NLDO is a key issue. Currently, there is no mechanism available to stop the blockage of 131I uptake in the nasolacrimal ducts via the NIS during 131I therapy,3 and there is scant data available regarding the prophylactic use of 2-(S)-(3-aminopropylamino) ethylphosphorothioic acid (amifostine) during 131I therapy.18 Further, the effectiveness of topical saline drops, nasolacrimal duct massage,
Table 2 Different case studies and reports of radioiodine-naive NLDO reported in the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Total patients treated</th>
<th>N with 131I therapy</th>
<th>Mean individual 131I dose (mCi)</th>
<th>Onset from last 131I therapy (months)</th>
<th>Treatment</th>
<th>Symptoms</th>
<th>Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kloos et al5</td>
<td>10 (2.6%)</td>
<td>10</td>
<td>180±15</td>
<td>(range: 3–16)</td>
<td>Observation (5 years), DCr (40%)</td>
<td>Epiphora, bilateral (50%)</td>
<td>Complete (60%)</td>
</tr>
<tr>
<td>Sun and Hatipoglu6</td>
<td>17</td>
<td>1</td>
<td>571±20</td>
<td>(range: 13–74)</td>
<td>Observation (30%), Balloon dilation (30%), DCr (40%)</td>
<td>Epiphora, bilateral (50%), Epiphora, unilateral (35%)</td>
<td>Partial (40%)</td>
</tr>
<tr>
<td>Fonseca et al7</td>
<td>26 (4.6%)</td>
<td>1</td>
<td>150±50</td>
<td>(range: 30–80)</td>
<td>Balloon dilation (40%), DCr (100%)</td>
<td>Epiphora, bilateral (50%), Epiphora, unilateral (35%)</td>
<td>Complete (80%)</td>
</tr>
<tr>
<td>Shepler et al8</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>700±100</td>
<td>(range: 50–90)</td>
<td>Observation (5 years), DCr (13%)</td>
<td>Epiphora, bilateral (50%), Epiphora, unilateral (35%)</td>
<td>Complete (82.4%)</td>
</tr>
<tr>
<td>Savage et al9</td>
<td>12 (2.3%)</td>
<td>12</td>
<td>479±45</td>
<td>(range: 39–72)</td>
<td>Observation (65–20), DCr (94.7%)</td>
<td>Epiphora, bilateral (50%), Epiphora, unilateral (35%)</td>
<td>Complete (78.9%)</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean or mean ± standard deviation, except where otherwise indicated.

Abbreviations: 131I, radioactive iodine 131; N, number; mCi, millicurie; DCr, dacryocystorhinostomy.

References

Conclusion
In conclusion, NLDO following 131I therapy in DTC patients is an under-recognized and rare complication, especially at higher 131I doses (>150 mCi). A multidisciplinary approach (nuclear medicine/oncology, ear, nose, and throat, and ophthalmology) is very important in the prevention and treatment of NLDO.

Author contributions
KHAQ and MAA designed the concept of the study. MAT, MAA, and YB carried out data collection; NJA, IM, and AAA carried out manuscript writing. MAT, YB, and AAA performed statistical analysis. All authors read and approved the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.


