Utility of PET in Head and Neck Cancer

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Abstract: Background. This study evaluates the utility of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) in patients with a node-positive mucosal head and neck squamous cell carcinoma who achieved a complete response at the primary site but had a residual mass in the neck 8 weeks or more after definitive (chemo)radiotherapy.

Methods. Between October 1996 and July 2002, 39 eligible patients were identified. The reference PET scan was performed at a median of 12 weeks (range, 8–32 weeks) after treatment.

Results. PET showed no metabolic activity in the residual mass in 32 patients. Five of these patients had a neck dissection and were all pathologically negative. The remaining 27 patients were observed for a median of 34 months (range, 16–86 months), with only one locoregional failure. The negative predictive value of PET for viable disease in a residual anatomic abnormality was 97%.

Conclusion. Patients who have achieved a complete response at the primary site but have a residual abnormality in the neck that is PET negative approximately 12 weeks after treatment do not require neck dissection and can be safely observed.

Keywords: PET; head and neck; squamous cell cancer; radiotherapy; chemotherapy

Positron emission tomography (PET) is a functional imaging tool that is being used increasingly in the staging, therapeutic monitoring, and restaging of many malignancies.1,2 Fluorine-18
fluorodeoxyglucose (FDG), an analog of glucose, has high uptake in a wide range of tumors relative to surrounding normal tissues.\textsuperscript{3,4}

Head and neck cancer accounts for approximately 5\% of all malignancies, with squamous cell carcinoma (SCC) being the major histologic subtype. Approximately 60\% of patients have locally advanced disease, usually treated with either surgery and postoperative radiotherapy or concomitant chemoradiotherapy.\textsuperscript{5–7}

In patients treated definitively with radiotherapy with or without chemotherapy [(chemo)radiotherapy], posttreatment management of the neck is controversial, with some authorities advocating a planned neck dissection on all patients whose initial nodal classification was N2A or N3.\textsuperscript{8,9} Although good evidence exists to show that this is unnecessary in patients who achieve a complete clinical and radiologic response, standard contemporary practice would call for at least a selective neck dissection in patients who are left with a residual palpable or CT imageable mass 8 weeks or more after the completion of treatment.\textsuperscript{10,11}

Because of the high specificity and sensitivity of FDG PET in detecting lymph node metastases before treatment, we undertook this study to assess the utility of PET in detecting viable tumor in nodes that had shown continuing but incomplete regression after radical treatment.\textsuperscript{12–14}

The ultimate aim of the study was to validate the safety of continued observation of patients whose PET scan showed no metabolic activity in the residual mass as opposed to surgical intervention.

Ware et al\textsuperscript{15} have reported our experience on the value of PET for post-therapy assessment in a more disparate patient population.\textsuperscript{15} The eligibility criteria for the previous study included clinical or radiologic suspicion of residual or recurrent disease in either or both the primary site and neck after either surgery or definitive (chemo)radiotherapy for a mucosal head and neck SCC (HNSCC) and the potential suitability for salvage therapy. The positive and negative predictive values were 95\% and 83\%, respectively. A subset of patients reported in this series (\(n = 12\)) was also reported in the Ware article. This report differs in that it has a longer accrual period, it is confined to and reports on an expanded number of patients with residual structural abnormalities in the neck after complete response at the primary site, and it does not include patients treated initially with surgery or patients with recurrent abnormalities.

**PATIENTS AND METHODS**

**Eligibility and Patient Characteristics.** Between October 1996 and July 2002, 315 patients with a mucosal HNSCC underwent a staging and/or restaging PET scan at our center. To be eligible for this study, patients had to have the following characteristics:

- Node-positive stage III to IV (American Joint Committee on Cancer Staging, 5th Edition) mucosal HNSCC treated definitively with radical (chemo)radiotherapy.\textsuperscript{16}
- Complete regression of the primary tumor but residual palpable and/or CT imageable neck mass 8 weeks or more after the completion of treatment.
- FDG PET scan performed to assess the presence of viable tumor in the residual neck mass.
- Pathologic confirmation or sufficient follow-up (>12 months) to allow clinical assessment of true neck status.

Thirty-nine patients were identified from the Peter MacCallum Cancer Centre prospective PET database as fulfilling the eligibility criteria. There were 29 men and 10 women, with a median age of 55 years (range, 37–89 years). The primary mucosal sites were oropharynx (\(n = 31\)), supraglottic larynx (\(n = 5\)), and hypopharynx (\(n = 3\)). All patients had stage III to IV disease, and 26\% had N3 disease. The T and N distribution is shown in Table 1.

**Treatment Details.** All patients received radiotherapy with or without chemotherapy.

Patients were simulated supine in a cobex cast and treated with 6-MV photon beam irradiation. Treatment techniques were based on the site of disease and potential areas of spread. In patients treated with parallel opposed photon beams, orthogonal simulator films were used for planning.

**Table 1.** T and N distribution (AJCC 5\textsuperscript{th} Edition).

<table>
<thead>
<tr>
<th>N status</th>
<th>No. patients by T classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 1 0 0 1</td>
</tr>
<tr>
<td>2a</td>
<td>1 5 3 0 9</td>
</tr>
<tr>
<td>2b</td>
<td>2 3 1 2 8</td>
</tr>
<tr>
<td>2c</td>
<td>0 3 7 1 11</td>
</tr>
<tr>
<td>3</td>
<td>3 6 0 1 10</td>
</tr>
<tr>
<td>Total</td>
<td>6 18 11 4 39</td>
</tr>
</tbody>
</table>

Abbreviation: AJCC, American Joint Committee on Cancer.
with off-cord photon field reductions and posterior electron strips used to keep the spinal cord dose ≤45 Gy. In patients for whom unilateral treatment was appropriate, CT planning was used. The site of gross disease (primary site and gross nodal involvement) was treated with a 1.5-cm to 2.0-cm margin, whereas all neck nodes suspected of harboring subclinical disease were treated electively. Radiation was delivered with a shrinking field technique.

Thirty-five patients were treated to 70 Gy in 2-Gy fractions over 7 weeks, with concurrent chemotherapy in 34 patients and without chemotherapy in one patient. Of the patients receiving concurrent chemoradiotherapy, 22 were treated with “chemoboost” in the final 2 weeks of radiation. This regimen has been described previously by Corry et al.17 In 19 patients, the planned “chemoboost” consisted of cisplatin (50 mg/m² day 1 of weeks 6 and 7 of radiation) and 5-fluorouracil (5-FU; 360 mg/m²/day continuous infusion day 1–5 of weeks 6 and 7 of radiation); one of these patients also received two cycles of induction chemotherapy with cisplatin (100 mg/m² day 1) and 5-FU (1000 mg/m² days 1–5) at a 21-day interval. Because of contraindications, three patients had the cisplatin substituted with carboplatin (area under the curve [AUC] 2.5 day 1). In 12 patients, concurrent chemotherapy consisted of cisplatin 75 mg/m² on day 2 of weeks 1, 4, and 7 and tirapazamine 290 mg/m² before each cisplatin dose and 160 mg/m² on days 1, 3, and 5 of weeks 2 and 3 of radiation. This regimen has been described previously by Rischin et al.18

Four patients were treated with altered fractionation, concomitant boost (n = 3) and accelerated radiotherapy (n = 1). Patients treated with concomitant boost received 50 Gy in 2-Gy fractions over 5 weeks to the gross disease and elective nodal regions, and in the final 2 weeks the gross disease received a second daily dose (minimum 6-hour interval) of 1.6 Gy, to give a total dose of 66 Gy in 35 fractions over 5 weeks. One patient was treated with accelerated radiotherapy (59.4 Gy in 33 fractions over 23 days). The median dose for the entire group was 70 Gy (range, 59.4–70 Gy).

**Positron Emission Tomography.** Patients underwent PET scanning with a GE Quest 300-H scanner (UGM Medical Systems, Inc., Philadelphia, PA). Details of the scanner characteristics and processing methods have been previously described.19–21 Patients routinely fasted a minimum of 6 hours before and were relaxed with intravenous diazepam (5–10 mg) to reduce physiological muscular uptake. Fluorine-18 FDG was injected 60 minutes before scanning. Whole-body scans were performed and emission data processed by use of iterative reconstruction both with and without attenuation correction.

**Statistical Methods.** All patients were accounted for in the analyses. Follow-up time was calculated from the date of presentation to the date of the last contact or death. Time to failure (primary, neck, or distant) was calculated from the date of presentation until the relevant event. Negative predictive value is the conditional probability that a patient was true negative for disease in the node, given that the PET scan result was negative. Positive predictive value is the conditional probability that a patient was true positive for disease in the node, given that the PET scan result was positive.

The study was approved by the hospital’s clinical research committee and ethics committee. All treated patients provided informed consent.

**RESULTS**

**Patient Outcomes.** The median potential follow-up time from presentation was 34 months (range, 16–86 months).

Twenty-six patients were alive at the time of analysis. All patients alive at the time of analysis were failure free.

There were 13 deaths; two of these patients had locoregional disease, and the remaining 11 died from the following causes (all were disease free locoregionally): distant metastases (n = 7), second primary tumor (n = 2; both lung), and unrelated causes (n = 2). No deaths occurred within 16 months of presentation.

Second cancers developed in four patients: lung (n = 2), floor of mouth (n = 1), and breast (n = 1).

**Timing of Positron Emission Tomography after Completion of Treatment.** Thirty-one patients (79%) underwent the posttreatment PET scan within 8 to 12 weeks after definitive (chemo)radiotherapy, with a median time of 12 weeks (range, 8–32 weeks).

The median size of the dominant residual neck mass, on the basis of CT and/or clinical examination about the time of PET scanning, was 1.5 cm (range, 0.8–3.5 cm). Eighty-seven percent of CT scans were performed within 6 weeks of the PET.
Predictive Value of Positron Emission Tomography.

**Negative Predictive Value for Residual Viable Nodal Disease.** Thirty-two patients had a negative PET for residual nodal disease. Of these, five had a neck dissection and were all pathologically negative. This group had no neck or primary tumor failures. One patient had distant metastasis develop at 25 months.

The remaining 27 patients were observed closely as the residual mass regressed and then followed routinely for a median of 34 months (range, 16–86 months). There were five failures: four patients had a distant recurrence (6, 15, 15, and 30 months), and one patient had recurrences simultaneously at the primary site and in the neck (8 months). No patients had isolated neck recurrences.

The number of true negatives was 31, and the number of false negatives was one, determined on the basis of pathologic analysis, clinical observation, or both. The negative predictive value of PET for viable disease in a residual neck node at least 8 weeks after treatment was 97% (Figure 1).

**Positive Predictive Value for Residual Viable Nodal Disease.** Seven patients were PET positive for residual nodal disease. All seven patients underwent a neck dissection, which was pathologically positive in five (true positive) and pathologically negative in two (false positive). The false-positive scans were both performed 12 weeks after treatment. In both cases, pathology reported the presence of degenerate keratinized squamous cells, multinucleated giant cells, and an inflammatory response. The pathologist believed that these cells represented cytoskeletons and were nonviable cells unlikely to have the ability to undergo replication and cell division. However, for the purposes of this study, these two cases were considered false positive. There were three failures: distant \((n = 2); 8\) and \(12\) months) and primary site and ipsilateral neck \((n = 1); 7\) months), all in patients with pathologically positive necks and positive results on PET scan.

The positive predictive value of PET for viable disease in a residual neck node at least 8 weeks after treatment was 71% if the two cases with “nonviable SCC” were included as false positives but 100% if they were to be considered true positives. Patient outcomes on the basis of PET scan results are shown in Figure 1.

**Detection of Distant Disease by Positron Emission Tomography.** In four patients, PET scans performed to evaluate the neck revealed asymptomatic distant metastases. All these patients subsequently died without locoregional failure.

**DISCUSSION**

The high sensitivity and specificity of FDG PET for the detection of disease before definitive treatment has been well documented.\(^{13,14,22}\) However, its role in assessing residual abnormalities after (chemo)radiotherapy remains unresolved. In this study the utility of PET in detecting disease in a residual neck node, at least 8 weeks after (chemo)-radiotherapy in patients who have achieved a complete response at the primary site, was evaluated. The optimal timing of the posttreatment PET in head and neck cancer remains undefined. The timing is a balance between a number of competing factors, which include allowing sufficient time for resolution of the post-radiotherapy inflammatory response (to minimize false-positive results) and for residual disease to reach the threshold of resolution by PET (to minimize false-negative results), while at the same time not unduly delaying surgical intervention if required. Performing a PET scan too early (<8 weeks) can result in less accurate results. For example, Rogers et al\(^{23}\) reported five of six false-negative results in patients scanned 4 weeks after treatment. Repopulation occurs rapidly in head and neck cancer, with a median time to clinical recurrence of 6 months. In view of this, by 12 weeks the resolution of PET should be sufficient to detect unsterilized disease. Kubota et al\(^{24}\) reported a 91% negative predictive value in 43 lesions of 36 patients scanned 4 months after treatment. On the basis of the preceding factors,
our unit favors initial posttreatment scanning between 8 and 12 weeks. It should be noted that our protocol provides for repeat PET scanning in patients whose residual anatomic abnormality stops regressing. In most cases, however, PET scanning at 8 to 12 weeks provides definitive information for clinical decision making. This timing has the added advantage that in the event a neck dissection is required, it can be performed before the onset of significant neck fibrosis, which may occur after high-dose chemoradiotherapy for large neck masses.

Our study demonstrates a high negative predictive value for FDG PET. All the patients who underwent neck dissection after a negative PET scan were pathologically negative. In the remaining patients, the accuracy of PET was determined by clinical follow-up. Basing a true negative finding on clinical follow-up rather than on the pathologic examination may be criticized on the grounds that the result is partly dependent on the length of follow-up. However, the median follow-up in this cohort of patients was 34 months (minimum, 16 months), which is more than sufficient time for most nodes harboring residual SCC to have declared themselves. Another potential criticism is that patients who died from distant metastases may have succumbed before manifesting neck disease. However, no patients in this group died of distant disease less than 16 months from presentation. Most importantly, no patients in this series sustained an isolated neck recurrence that could have been prevented by neck dissection.

On the basis of emerging data, a planned neck dissection after radical radiotherapy for patients with >3-cm neck nodes would seem to be obsolete if a complete clinical and radiologic response is achieved in the neck.10,11

The concept of a planned neck dissection was developed on the basis of poor control rates achieved for N2 to N3 neck disease after definitive conventionally fractionated radiotherapy. However, improved radiotherapy techniques, altered fractionation, and chemoradiotherapy regimens have resulted in higher complete response rates for advanced nodal disease. Both Peters et al10 and Johnson et al11 reported a low risk (5%) of isolated neck failure after radiotherapy if a complete clinical response in the neck was achieved. In the Peters et al study, when patients initially seen with node(s) 3 cm were compared with those with nodes >3 cm, there was no significant difference in control rates if a complete response was achieved.10 Both authors argue it is safe to observe the neck if a complete response is achieved. Given the high local complication rate with radiotherapy to the neck followed by neck dissection (17% to 35%), neck surgery should be avoided if it is unnecessary (no residual disease) or futile (uncontrolled disease present beyond the neck).25–27

The use of combined chemoradiotherapy schedules is likely to result in higher response rates in the neck compared with radiotherapy alone. Garden et al,28 using chemoradiotherapy, achieved a complete response in 27 (47%) of 57 patients with no isolated neck failures. The combination of radiotherapy with novel drugs such as tirapazamine, a hypoxic cell cytotoxin, is providing encouraging results and is currently being assessed in an phase III randomized international study for locally advanced mucosal HNSCC.18

The dilemma remains in assessing a complete response. Many of the early studies assessed response to radiotherapy on clinical examination, which is highly observer dependent. Some authors support the strong view that response rate should be based not only on clinical examination but also CT findings at least 8 weeks after treatment.29 Radiologic assessment after definitive radiotherapy with structural imaging may report on equivocal (~1 cm) residual node(s). Given the accuracy of FDG PET in detecting pathologically involved nodes in head and neck cancer preoperatively, its potential role in assessing the “equivocal node” reported on structural imaging after definitive radiotherapy is enticing. The high negative predictive value of PET that we have demonstrated in this setting supports the policy of observing the neck.

How PET imaging can have such a high negative predictive value when the resolution of PET is 5 to 7 mm is intriguing. The most likely explanation is based on the biologic phenomenon of accelerated repopulation of cancer cells that are not sterilized by treatment.30 Because PET scans were performed with a minimum 8-week and median 12-week interval after treatment, it can be hypothesized that if residual viable tumor cells did remain after treatment, they would have repopulated to a size resolvable by PET within this time frame.

The positive predictive value of PET in our study was not as high as reported in other series.31 There are a number of possible explanations for this. The number of patients who were positive in the neck was low, and, therefore, only
a small number of false positives was required to give a lower than expected positive predictive value. Ongoing inflammation within the nodes can result in a positive PET scan, and it is interesting to note that both false-positive cases in our series were considered to have “nonviable” tumor remnants that may have provoked an inflammatory response.

Because most of our patients underwent a PET scan 12 weeks after treatment, our current policy of management of the neck in patients with nodal disease who are treated with definitive (chemo)radiotherapy and ultimately achieve a complete response at the primary site up to 8 weeks after treatment is shown in Figure 2. Patients undergo review 4 weeks after treatment. At 8 weeks, if there has been a complete response at the primary site but an increase or no change in pretreatment nodal size, early neck dissection is recommended. If the nodal size is reduced or there has been a complete response, patients are reassessed again at 12 weeks, clinically and with CT. If both are negative, the patient is observed. If there is a neck mass palpable or a residual node seen on CT, a PET scan is performed. If the PET scan is negative, patients continue on monthly observation until regression to <1 cm occurs. This may take several months. If the mass ceases to regress in 2 consecutive months, but remains stable >1 cm, a further PET scan is obtained. If either the 12-week PET scan or a subsequent scan is positive, a limited neck dissection is performed.

Finally, comment should be made on the incremental value of PET scanning at 12 weeks in detecting asymptomatic distant metastases in 10% of our patients. Fogarty et al32 also reported the usefulness of PET in detecting unsuspected metastases in patients with carcinomas of an unknown primary tumor.

CONCLUSION

FDG PET has a high negative predictive value in patients with a residual neck node after (chemo)-radiotherapy. Patients who have achieved a complete response at the primary site but have a residual anatomic abnormality in the neck that is negative on PET scan approximately 12 weeks after treatment do not require neck dissection and can be safely observed.

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REFERENCES