Oncologic Outcomes for Head and Neck Skin Malignancies Treated with Protons

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Abstract

Purpose: Radiation therapy (RT) is the standard treatment for patients with inoperable skin malignancies of the head and neck region (H&N), and as adjuvant treatment post surgery in patients at high risk for local or regional recurrence. This study reports clinical outcomes of intensity-modulated proton therapy (IMPT) for these malignancies.

Materials and Methods: We retrospectively reviewed cases involving 47 patients with H&N malignancies of the skin (squamous cell, basal cell, melanoma, Merkel cell, angiosarcoma, other) who underwent IMPT for curative intent between July 2016 and July 2019. Overall survival was estimated via Kaplan-Meier analysis, and oncologic outcomes were reported as cumulative incidence with death as a competing risk.

Results: The 2-year estimated local recurrence rate, regional recurrence rate, local regional recurrence rate, distant metastasis rate, and overall survival were 11.1% (95% confidence interval [CI], 4.1%-30.3%), 4.4% (95% CI, 1.1%-17.4%), 15.5% (95% CI, 7%-34.3%), 23.4% (95% CI, 5.8%-95.5%), and 87.2% (95% CI, 75.7%-100%), respectively. No patient was reported to have a grade 3 or higher adverse event during the last week of treatment or at the 3-month follow-up visit.

Conclusion: IMPT is safe and effective in the treatment of skin malignancies of the H&N.

Keywords: skin cancer; intensity-modulated proton therapy; oncologic outcomes; adverse events

Introduction

Surgical excision is the primary treatment for carcinomas and sarcomas of the skin [1–5]. However, radiation therapy (RT) is used in some situations, such as patients with disease in the head and neck region for whom surgery may result in cosmetic and/or functional deficits, patients with unresectable disease, or patients with multiple medical comorbidities. Radiation therapy also plays a role as an adjuvant treatment following surgery in patients with close or positive margins, satellite tumors, deep invasion, high-grade
malignancies, bone or cartilage invasion, perineural invasion, lymph node metastases, extranodal extension, or recurrent
disease.

There are several RT techniques for treating cutaneous lesions, including orthovoltage photons, 3-dimensional photon
therapy, intensity-modulated photon radiation therapy (IMRT), electrons, and intensity-modulated proton radiation therapy
(IMPT).

For scalp lesions, the dose distribution of electrons and orthovoltage RT is not conformal along the curved surfaces of the
scalp. Large targets will require matched fields with these techniques, which are likely to introduce severe inhomogeneity.
IMRT can conform dose to curved surfaces, resulting in increased homogenous tumor coverage as compared with other RT
techniques [6–10]. However, the penetrating nature of megavoltage RT used by IMRT can lead to increased doses to the
underlying brain [7–9] and eyes [7, 8] as compared with other RT techniques.

Ipsilateral neck RT in patients with skin lesions is indicated for treating primary lesions in the neck and for treating regional
nodes, which requires exclusion of organs of the upper aerodigestive tract from the treatment volume. IMRT provides good
dose conformity to the target volume. However, the integral dose to normal organs in the central or contralateral regions of the
neck results in toxicity [11–14].

For larger lesions involving the face, IMRT is preferred because it can confine dose within the tumor target volume and
restrict dose to the eyes, oral cavity, pharyngeal mucosa, and salivary glands. IMRT is also a recommended RT technique for
tumors with cranial nerve invasion because nerve pathways to the skull, cavernous sinus, and brainstem are close to critical
sensitive structures [15, 16]. However, IMRT has the limitation of entrance and exit dose in adjacent normal organs [17]. In
some patients who have gross disease close to critical normal organs, it is extremely difficult to increase dose to a therapeutic
level while keeping an acceptable dose constraint to the adjacent critical normal organs.

IMPT can produce conformal dose distributions around the tumor target volume like IMRT, but the distal dose is truncated,
sparing adjacent structures from collateral dose. Therefore, it is expected in some situations that toxicities can be minimized by
using IMPT for skin carcinomas and sarcomas in the head and neck region, compared with other RT modalities.

Previous studies of proton RT for treating patients with head and neck cancer, which included a small number of patients
with skin malignancies, showed at least similar or better dose distributions in the tumor target volume [11, 18–22] with less
dose to adjacent normal structures [11, 19–29] when compared to patients who were treated with IMRT. However, we are in
need of data to confirm whether the dosimetric advantages from IMPT can result in clinical advantages.

To date, there are limited studies documenting the clinical outcome of patients with skin malignancies in the head and neck
region treated with IMPT. The aim of this study is to provide oncologic outcomes of patients with skin carcinomas and
sarcomas in the head and neck region treated with IMPT. A subsequent article will report patient-reported outcomes related to
organ-at-risk dose-volume histogram statistics.

Materials and Methods

Study Design and Patient Population

This study is a retrospective study of skin carcinomas and sarcomas of the head and neck region treated with curative-intent
IMPT between July 2016 and July 2019. The study was approved by the Institutional Review Board. Patients were excluded
from analysis if they had previous RT to the same area, they did not give consent for their medical records to be used for
research, they did not receive a complete course of IMPT, or they were treated with a mixture of photons and protons. Forty-
seven patients were included. Demographic data, disease and treatment details, and patient status were extracted from the
electronic health records.

Treatment Details

Radiation therapy

All patients underwent computed tomography (CT) simulation with a customized head and neck rest, thermoplastic mask,
and intraoral device for immobilization. Bolus helmets were used for proton energy degradation and optimizing beam spot size
for superficial tumors that were close to critical organs, such as ocular structures. The relative biological equivalent of 1.1 was
used for proton dose calculation. Commonly prescribed dose regimens are shown in Table 1.
For regions at intermediate or low risk of tumor extension, such as elective lymph nodes, a lower dose was prescribed. Stereotactic radiosurgery was used as a boost technique for intracranial gross tumor extension in 3 patients. Treatment volumes were determined and contoured by the treating radiation oncologist depending on the risk of microscopic tumor extension. If there were risks for cranial nerve involvement the nerves at risk were contoured retrogradely to the brain stem. Robust optimization was used with 3- to 5-mm translational setup uncertainties and 3% to 5% range uncertainties. The treatment planning system was Varian Medical System’s Eclipse (Varian Medical Systems, Palo Alto, California).

IMPT planning used proton convolution superposition or an in-house Monte Carlo–based algorithm called Spock. Image-guided RT was performed daily by using 2D-3D kV imaging with 6-degrees-of-freedom couch adjustments with an option for in-room CT on rails volumetric verification. Weekly CT verification scans were performed on the in-room CT on rails with the patient in the treatment position, and replanning was performed when the target volume that received at least 95% of the prescribed dose (V95%) was < 95% or when a high-priority organ-at-risk dose deviation was > 5% or when a low-priority organ-at-risk dose deviation was > 10%.

Systemic therapy and surgery
All patients underwent multidisciplinary evaluation. Patients who were appropriate surgical candidates were treated with surgery. Most patients who received surgery at outside hospitals had their pathology specimens reviewed at Mayo Clinic and a surgeon was consulted if there was a concern for margin status. The aim of surgery for skin malignancies was to remove the tumor with negative margins and still maintain acceptable cosmesis, function, and quality of life. Systemic treatment was determined by the consulting medical oncologist. For 9 patients with squamous cell carcinoma, 5 were treated with concurrent cisplatin, 2 were treated with concurrent cemiplimab, 1 was treated with induction and concurrent cemiplimab, and 1 was treated with induction carboplatin, paclitaxel, and cetuximab and concurrent cisplatin. For 3 patients with melanoma, 1 was treated with adjuvant nivolumab following IMPT and 2 were treated with concurrent and adjuvant nivolumab.

Adverse Events
Provider-reported adverse events related to IMPT were recorded prospectively during the last week of treatment and at the 3-month, 6-month, and 12-month follow-up visit by using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (National Cancer Institute, Bethesda, Maryland).

Statistical Methods
The events of interest were local recurrence, regional nodal recurrence, local regional recurrence, distant metastasis, and overall survival.

Patient characteristics, pathology, and dosimetry data are reported as median (interquartile range [IQR]) or percentage (N) as appropriate. Local recurrence, regional nodal recurrence, local regional recurrence, distant metastasis, and overall survival were calculated as the time from the last day of IMPT treatment to the date of the event or death. Recurrence and metastasis rates were estimated by using a competing risks model, and overall survival was estimated by using the Kaplan-Meier method. Effects of predictors were estimated by using Cox proportional hazards regression. Statistical significance was defined as $P < .05$. Statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, North Carolina).
Results

Patient and Tumor Characteristics
Forty-seven patients were treated with IMPT. The median age was 72.8 years (IQR, 68.2-78.5). Eighty-five percent of patients were men. Sixty-eight percent of patients were diagnosed with squamous cell carcinoma. Other histologic types included melanoma, basal cell carcinoma, angiosarcoma, and Merkel cell carcinoma in 14.9%, 4.3%, 6.4%, and 2.1% of patients, respectively. The tumor location was in area M (cheek, forehead, scalp, and neck) in 62.5% of patients, and in area H (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, periauricular, and postauricular) in 37.5%. In approximately 50% of patients, primary and nodal classification could not be assessed. The details of patient and tumor characteristics are shown in Table 2.

Treatment Characteristics
Most patients were treated with surgery combined with IMPT with or without chemotherapy (surgery+IMPT, 59.6%; surgery+IMPT+chemotherapy, 14.9%). Chemotherapy was prescribed in 31.9% of patients. The median dose used was 60 Gy (IQR, 60-66). Three patients received a stereotactic radiosurgical boost for gross intracranial tumor extension with a median dose of 12 Gy (IQR, 10-12). The treatment volumes were grouped into ipsilateral neck (55.3%), scalp (25.5%), and face (17%). The median clinical target volume (CTV) for the high-dose region was 106 cm³ (IQR, 20-308). The median percentage of prescribed dose to 95% (D95%) of the high-risk CTV was 100% (IQR, 99%-101%). The details of treatment characteristics are shown in Table 3.

Oncologic Outcomes
The median follow-up time was 1.31 years (IQR, 0.56-1.56). The details of disease recurrence and death are shown in Table 4.

Univariable Analysis
Univariable analysis revealed that treatment with surgery and postoperative adjuvant IMPT was associated with lower risk for local recurrence and local regional recurrence than IMPT alone. None of the other factors evaluated were found to be associated with local recurrence, regional nodal recurrence, local regional recurrence, distant metastasis, or death as shown in Table 5. A multivariable analysis was not performed owing to the small number of events.

Adverse Events
No patient was reported to have a grade 3 or higher adverse event during the last week of treatment or at the 3-month follow-up visit, including ocular toxicity, radiation dermatitis, dry mouth, dysgeusia, mucosal infection, oral pain, pharyngolaryngeal pain, salivary duct inflammation, brain necrosis, or osteoradionecrosis.

For grade 2 adverse events reported during the last week of treatment, 9 patients were reported to have radiation dermatitis, 3 dysgeusia, 3 oral pain, 2 pharyngolaryngeal pain, 2 dry mouth, 2 salivary duct inflammation, 2 ocular toxicity, and 1 mucosal infection. At the 3-month follow-up visit, 2 patients were reported to have grade 2 dry mouth, 1 skin ulceration with infection, and 1 dysgeusia.

Discussion
This retrospective early report of skin malignancies of the head and neck region treated with IMPT suggests that IMPT is safe and effective in providing local and regional control of disease, particularly in the adjuvant setting for advanced disease.
Table 2. Patient and tumor characteristics.

| Characteristics                          | IMPT (n = 47) |
|------------------------------------------|---------------|
| Age, median (IQR), y                     | 72.8 (68.2-78.5) |
| Sex, % (n/total)                         |               |
| Male                                     | 85.1 (40/47)  |
| Female                                   | 14.9 (7/47)   |
| Histologic type, % (n/total)             |               |
| Squamous cell carcinoma                  | 68.1 (32/47)  |
| Basal cell carcinoma                     | 4.3 (2/47)    |
| Melanoma                                 | 14.9 (7/47)   |
| Merkel cell carcinoma                    | 2.1 (1/47)    |
| Angiosarcoma                             | 6.4 (3/47)    |
| Othersa                                  | 4.3 (2/47)    |
| Disease status (before IMPT), % (n/total)|               |
| First diagnosis                          | 53.2 (25/47)  |
| Recurrent disease                        | 46.8 (22/47)  |
| Location of tumor, % (n/total)           |               |
| Area Mb                                  | 62.5 (25/40)  |
| Area Hc                                  | 37.5 (15/40)  |
| Missing                                  | n = 7         |
| Largest tumor size, median (IQR), cm     | 3 (2-4)       |
| Depth of invasion, median (IQR), mm      | 12 (4-20)     |
| T classification at initial diagnosisd, % (n/total) |          |
| TX                                       | 48.9 (23/47)  |
| T0/T1/T2                                 | 27.7 (13/47)  |
| T3/T4                                    | 23.4 (11/47)  |
| N classification at initial diagnosisd, % (n/total) |          |
| NX                                       | 46.8 (22/47)  |
| N0                                       | 34.0 (16/47)  |
| N1/N2/N3                                 | 19.1 (9/47)   |
| Perineural involvement, % (n/total)      |               |
| No                                       | 3.8 (1/26)    |
| Yes                                      | 96.2 (25/26)  |
| Missing                                  | n = 21        |
| Lymphatic involvement, % (n/total)       |               |
| No                                       | 50 (3/6)      |
| Yes                                      | 50 (3/6)      |
| Missing                                  | n = 41        |
| Vascular involvement, % (n/total)        |               |
| No                                       | 50 (3/6)      |
| Yes                                      | 50 (3/6)      |
| Missing                                  | n = 41        |
| Surgical margins, % (n/total)            |               |
| Negative (R0)                            | 71.4 (25/35)  |
| Positive (R1/R2)                         | 28.6 (10/35)  |
| Missing                                  | n = 12        |

Abbreviations: IMPT, intensity-modulated proton therapy; IQR, interquartile range; R0, negative margins; R1, microscopically positive margins; R2, gross residual disease.

*aOthers: dermatofibrosarcoma protuberans, pleomorphic dermal sarcoma.
*bCheek, forehead, scalp, neck.
*cCentral face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, periauricular, postauricular.
*dAJCC 8th edition,30 clinical and pathologic staging.
There is limited research investigating proton therapy for skin malignancies of the head and neck region. One small retrospective trial from Japan studied the results of proton therapy in 6 patients with skin carcinomas. Good tumor response (at least 90% tumor regression in all patients) was observed [31]. Romesser et al [19] conducted a retrospective study in 41 patients with major salivary gland cancer or skin squamous cell carcinoma treated with ipsilateral neck proton or photon RT. Comparing passive scattering proton RT to IMRT, they reported no difference in tumor dose coverage or 1-year local regional tumor control.

There are several limitations in this retrospective study. The length of follow-up is relatively short. Longer follow-up will be required to document long-term oncologic outcomes and late adverse events. However, these early results are promising. Tumor and nodal classification could not be assessed in approximately 50% of patients. The reason for the missing initial staging information was the lack of this information in the medical record, which could not be determined by any means for patients referred from outside our institution. Another limitation is the variety of malignancies including squamous cell carcinoma, basal cell carcinoma, melanoma, Merkel cell carcinoma, angiosarcoma, and other malignancies, which may have

Table 3. Treatment characteristics.

| Characteristics                  | IMPT (n = 47) |
|----------------------------------|---------------|
| Treatment regimen, % (n/total)   |               |
| IMPT alone                       | 8.5 (4/47)    |
| Surgery + IMPT                   | 59.6 (28/47)  |
| IMPT + chemotherapy              | 17.0 (8/47)   |
| Surgery + IMPT + chemotherapy    | 14.9 (7/47)   |
| IMPT indication, % (n/total)     |               |
| Definitive IMPT                  | 27.7 (13/47)  |
| Adjuvant IMPT                    | 72.3 (34/47)  |
| IMPT dose (GyRBE 1.1)            |               |
| Median (IQR)                     | 60 (60-66)    |
| Mean (SD)                        | 57.7 (12.26)  |
| IMPT region, % (n/total)         |               |
| Scalpa                          | 25.5 (12/47)  |
| Ipsilateral neck                 | 55.3 (26/47)  |
| Bilateral neck                   | 2.1 (1/47)    |
| Faceb                           | 17.0 (8/47)   |
| IMPT volume, median (IQR), cm³   |               |
| High-dose CTV                    | 106 (20-308)  |
| Intermediate-dose CTV            | 280 (140-519) |
| Low-dose CTV                     | 159 (46-528)  |
| D95% high-dose CTVc (%), median (IQR) | 100 (99-101) |

Abbreviations: IMPT, intensity-modulated proton therapy; IQR, interquartile range; CTV, clinical target volume.

aForehead and scalp.

bCentral face, eyelid, eyebrows, periorbital nose, lips, chin, mandible, cheek, periauricular, postauricular.

cPercentage of the prescribed dose that covered 95% of the CTV high-risk volume.

Table 4. Disease recurrence and death.

| Event                      | IMPT 2-year estimates, % (95% CI) |
|----------------------------|-----------------------------------|
| Local recurrence           | 11.1 (4.1-30.3)                   |
| Regional nodal recurrence  | 4.4 (1.1-17.4)                    |
| Local regional recurrence  | 15.5 (7.3-34.3)                   |
| Distant metastasis         | 23.4 (5.8-95.5)                   |
| Overall survival           | 87.2 (75.7-100)                   |

Abbreviation: IMPT, intensity-modulated proton therapy; CI, confidence interval.
differing disease control and survival outcomes. This is why we performed a separate analysis for the largest squamous cell carcinoma subgroup.

**Conclusion**

IMPT is safe and effective in providing local and regional disease control for patients with skin malignancies of the head and neck region.

**ADDITIONAL INFORMATION AND DECLARATIONS**

**Conflicts of Interest:** The authors have no relevant conflicts of interest to disclose.

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**Ethical Approval:** All patient data have been collected under institutional review board (IRB)–approved protocol.
Table 5. Hazard Ratio (95% Confidence Interval)

| Characteristic                        | Local recurrence (4 events) | Local regional recurrence (6 events) | Distant metastasis (4 events) | Overall survival (4 events) |
|--------------------------------------|----------------------------|-------------------------------------|-----------------------------|-----------------------------|
| Age, per y                           | 0.99 (0.92, 1.06)          | 0.98 (0.94, 1.03)                  | 1.02 (0.92, 1.14)           | 1.10 (0.95, 1.27)           |
|                                      | .70                       | .48                                 | .70                         | .21                         |
| Histologic type                      |                            |                                     |                             |                             |
| Non–squamous cell                    | 1.00 (reference)          | 1.00 (reference)                    | 1.00 (reference)            | 1.00 (reference)            |
| Squamous cell                        | 4.96 (0.19, 131)          | 2.68 (0.33, 21.97)                 | 1.07 (0.09, 12.31)          | 1.73 (0.18, 16.70)          |
|                                      | .34                       | .36                                 | .96                         | .64                         |
| Disease status                       |                            |                                     |                             |                             |
| First diagnosis                      | 1.00 (reference)          | 1.00 (reference)                    | 1.00 (reference)            | 1.00 (reference)            |
| Recurrent disease                    | 1.22 (0.18, 8.30)         | 2.55 (0.49, 13.21)                 | 3.01 (0.32, 28.01)          | 3.77 (0.39, 36.31)          |
|                                      | .84                       | .26                                 | .33                         | .25                         |
| Location of tumor                    |                            |                                     |                             |                             |
| Area M<sup>a</sup>                   | 1.00 (reference)          | 1.00 (reference)                    | 1.00 (reference)            | 1.00 (reference)            |
| Area H<sup>b</sup>                   | 3.19 (0.30, 33.37)        | 1.05 (0.19, 5.87)                  | 1.16 (0.20, 6.90)           | 0.46 (0.05, 4.47)           |
|                                      | .33                       | .96                                 | .87                         | .51                         |
| Largest tumor size, cm               | 0.60 (0.31, 1.18)         | 0.60 (0.35, 1.04)                  | 0.82 (0.46, 1.47)           | 0.50 (0.13, 1.89)           |
|                                      | .14                       | .07                                 | .51                         | .31                         |
| T classification<sup>c</sup>         |                            |                                     |                             |                             |
| Overall P                            | .73                       | .63                                 | NA                          | NA                          |
| T0/T1/T2                             | 1.00 (reference)          | 1.00 (reference)                    | NA                          | NA                          |
| TX                                   | 1.93 (0.18, 20.35)        | 2.54 (0.27, 23.74)                 | NA                          | NA                          |
|                                      | .59                       | .41                                 | NA                          | NA                          |
| T3/T4                                | 0.33 (0.01, 14.46)        | 1.21 (0.08, 19.64)                 | NA                          | NA                          |
|                                      | .80                       | .89                                 | NA                          | NA                          |
| N classification<sup>c</sup>         |                            |                                     |                             |                             |
| Overall P                            | NA                        | .56                                 | .69                         | .84                         |
| N0                                   | NA                        | 1.00 (reference)                    | 1.00 (reference)            | 1.00 (reference)            |
| NX                                   | NA                        | 2.52 (0.25, 25.41)                 | 4.32 (0.13, 143)            | 0.92 (0.13, 6.61)           |
|                                      | NA                        | .43                                 | .41                         | .93                         |
| N1/N2/N3                             | NA                        | 3.68 (0.34, 39.60)                 | 4.76 (0.11, 207)            | 0.35 (0.01, 12.39)          |
|                                      | NA                        | .28                                 | .42                         | .57                         |
| Surgical margins                     |                            |                                     |                             |                             |
| Negative                             | 1.0 (reference)           | NA                                  | NA                          | 1.0 (reference)             |
| Positive                             | 2.62 (0.18, 38.79)        | NA                                  | NA                          | 0.76 (0.01, 74.54)          |
|                                      | .48                       | NA                                  | NA                          | .91                         |
| Treatment regimen                    |                            |                                     |                             |                             |
| Overall P                            | .14                       | .20                                 | .33                         | NA                          |
| IMPT alone                           | 1.00 (reference)          | 1.00 (reference)                    | 1.00 (reference)            | NA                          |
| Surgery+IMPT                          | 0.07 (0.01, 0.76)         | 0.14 (0.02, 0.93)                  | 0.13 (0.01, 1.71)           | NA                          |
|                                      | .03                       | .04                                 | .04                         | NA                          |
| IMPT+CT                              | 0.07 (0.01, 2.77)         | 0.24 (0.03, 2.26)                  | 0.09 (0.01, 4.94)           | NA                          |
|                                      | .15                       | .21                                 | .24                         | NA                          |
| Surgery+IMPT+CT                       | 0.24 (0.03, 1.98)         | 0.24 (0.03, 2.00)                  | 0.79 (0.08, 7.53)           | NA                          |
|                                      | .18                       | .19                                 | .84                         | NA                          |
| IMPT indication                      |                            |                                     |                             |                             |
| Definitive IMPT                       | 1.00 (reference)          | 1.00 (reference)                    | 1.00 (reference)            | 1.00 (reference)            |
| Adjuvant IMPT                         | 0.17 (0.02, 1.44)         | 0.19 (0.04, 1.03)                  | 1.36 (0.13, 14.20)          | 0.14 (0.01, 1.32)           |
|                                      | .10                       | .054                                | .80                         | .09                         |

Abbreviations: NA, not analyzed; IMPT, intensity-modulated proton therapy; CT, chemotherapy.

*Area M: cheek, forehead, scalp, neck (reference).

*Area H: central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, periauricular, postauricular.

*AJCC 8th edition, clinical and pathologic staging.
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