Seven-year follow-up demonstrating sustained survival following ^{125}I seed brachytherapy in an elderly patient with lip squamous cell carcinoma and Alzheimer's disease: A case report

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Abstract. Lip squamous cell carcinoma is a distinct subtype of oral malignancy. Surgical resection provides satisfactory local tumor control; however, it frequently compromises oral function, diminishes local sensation and disfigures facial contour-sequelae are disproportionately debilitating in elderly patients with multimorbidity. This study reported the case of an 80-year-old woman with Alzheimer's disease who presented with locally advanced lip squamous cell carcinoma (cT3N2bM0, stage IVA) and cervical lymph node metastases. Following multidisciplinary team evaluation, the patient was deemed unsuitable for curative surgical resection or definitive external-beam radiotherapy. Therefore, computed tomography (CT)-guided radioactive ^{125}I seed implantation, assisted by a three-dimensional (3D) printed template, was performed for both the primary lip tumor and the metastatic cervical nodes, with a prescribed dose of 140 Gy. Postprocedural dosimetric verification confirmed adequate target volume coverage. The patient achieved a durable clinical complete response, with remarkable tumor regression, preserved speech and swallowing function, and remains alive with overall survival exceeding 7 years. This case demonstrates the long-term efficacy and safety of the aforementioned minimally invasive approach in an elderly patient with severe cognitive impairment-a population routinely excluded from prospective trials. No radiation-related toxicities, including xerostomia or osteoradionecrosis, were documented during follow-up. These findings indicate that CT-guided ^{125}I seed brachytherapy with 3D-printed templates is a feasible, function-preserving and potentially curative treatment option for carefully selected elderly patients with advanced lip squamous cell carcinoma who are unable to tolerate conventional definitive therapy. These results further challenge the common view that interventional brachytherapy serves only as a palliative measure.

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Introduction

The 5-year survival rate for patients with oral cancer is ~80%, but it decreases to 40-50% in those with regional or distant metastasis (1). Lip squamous cell carcinoma constitutes 25-30% of all oral malignancies and can be effectively managed through various therapeutic modalities, including surgical resection, external-beam radiotherapy (EBRT). In locally advanced disease, treatment failure is characterized by high local recurrence (20-40%) and regional lymph node metastasis, both of which substantially worsen patient prognosis (2). Surgical resection remains the cornerstone of curative treatment for early-stage oral squamous cell carcinoma, and accumulating evidence supports multimodal strategies incorporating adjuvant radiotherapy to optimize oncological outcomes (3-5). However, extensive resection can lead to disfiguring defects and functional impairments, including mastication, swallowing and speech difficulties, whereas radical EBRT frequently entails serious complications such as osteoradionecrosis (ORN), xerostomia and intractable mucositis, all of which markedly compromise the quality of life of patients (6,7).

Conventional therapeutic approaches are often impractical in elderly patients with multiple chronic comorbidities. The patient described in this study was diagnosed with Alzheimer's disease. Consequently, neither surgery nor definitive EBRT could be performed. The cognitive impairment limited the

patient's ability to cooperate with postoperative rehabilitation and daily radiotherapy positioning. Furthermore, general anesthesia was associated with an unacceptably high risk of severe complications and the patient's family firmly declined any surgical intervention. The present case highlighted that there is an urgent unmet clinical need for alternative strategies that balance effective tumor suppression with preservation of organ function and quality of life in this high-risk elderly population.

Radioactive ^{125}I seed implantation has advanced rapidly in recent years, demonstrating broad applicability across various solid malignancies, including lung, pancreatic and liver cancers, as well as bone metastases (8-11). Accumulating evidence further supports the efficacy of this approach in head and neck malignancies. Li *et al* (12) reported the safety and efficacy of radioactive ^{125}I seed implantation as salvage therapy for locally recurrent head and neck soft-tissue sarcoma and Zhang *et al* (13) demonstrated its utility in inoperable head and neck cancers, whereas Tian *et al* (14) described ultrasound-guided radioactive ^{125}I seed implantation for oral squamous cell carcinoma, achieving favorable local control. These studies provide a key foundation for extending this technique to the treatment of lip squamous cell carcinoma in medically complex elderly patients. The present study aimed to report a case of lip squamous cell carcinoma in an elderly patient who presented with rapid tumor progression, severe pain and restricted mouth opening. Biopsy confirmed squamous cell carcinoma. The lesion showed marked clinical regression after radioactive ^{125}I seed implantation, leading to prolonged survival.

Case report

Case presentation. An 80-year-old woman presented to the Affiliated Zhongshan Hospital of Dalian University (Dalian, China) in September 2018 with a confirmed diagnosis of lip squamous cell carcinoma. The patient had a longstanding history of Alzheimer's disease, which had been diagnosed in 2010 and had gradually progressed to mild-to-moderate cognitive dysfunction. The Mini-Mental State Examination score was 18 of 30. The patient also had a 15-year history of hypertension and an 8-year history of type 2 diabetes mellitus, both adequately controlled with oral medications. The patient's regular regimen included donepezil 5 mg once daily, amlodipine 5 mg once daily and metformin 500 mg twice daily. The activities of daily living score was 60, indicating partial dependence on routine self-care.

Clinical findings. On admission, the patient's height was 155 cm, body weight 48 kg and body mass index 20.0 kg/m^2. The Nutritional Risk Screening 2002 score (15) was 3, suggesting mild malnutrition risk. In 2016, a soybean-sized mass had been incidentally noted on the lower lip. The patient remained asymptomatic and received no treatment at that time. However, by 2018, the mass had grown rapidly and become progressively painful, eventually causing gradual restriction of mouth opening (Fig. 1A). The patient had also developed food-evoked pain [visual analog scale (16): 6-7/10]. Due to having Alzheimer's disease, the patient could not complete independent self-rating; the pain evaluation was conducted with family assistance based on the patient's verbal description. Additional clinical manifestations included dysarthria and halitosis. Physical examination revealed a firm, immobile lower-lip lesion with ill-defined margins, mucosal ulceration and superficial bleeding. Palpation of the right neck revealed 5 enlarged lymph nodes, with a maximum diameter of up to 2 cm, which were firm and poorly mobile.

Diagnostic assessment. Contrast-enhanced computed tomography (CT) revealed a soft-tissue mass measuring 4.0 x 7.0 cm involving the midline-to-right aspect of the lower lip (Fig. 2A). The lesion invaded the vermilion border and underlying orbicularis oris muscle, with a maximum depth of invasion of 2.5 cm. A total of 12 enlarged lymph nodes were identified in levels II-III of the right neck, the largest measuring 1.7 cm in longitudinal diameter. No radiological evidence of distant metastasis was detected. Routine laboratory tests, including complete blood count, hepatic and renal function and coagulation parameters, were all within normal limits. However, the serum squamous cell carcinoma antigen level was markedly elevated at 4.2 ng/ml (normal upper limit <1.5 ng/ml). A preoperative biopsy of the lip lesion was performed for pathological evaluation. The specimen, measuring 0.8 x 0.5 x 0.3 cm, showed infiltrative nests of atypical squamous epithelial cells with keratin pearls and distinct intercellular bridges, which were consistent with the manifestations of moderately differentiated squamous cell carcinoma. Serial sections (4 μm) were prepared from formalin-fixed and paraffin-embedded tissue specimens. Hematoxylin and eosin (H&E) staining was automatically performed on a Roche staining system [Roche Diagnostics (Shanghai) Co., Ltd.] according to the manufacturer's recommended protocol for routine histomorphological assessment. All immunohistochemical (IHC) staining procedures were conducted using the Roche BenchMark ULTRA automated IHC platform (Roche Diagnostics). Sections were loaded onto the platform, where endogenous peroxidase activity was automatically blocked by the system during the IHC procedure. Heat-induced epitope retrieval was performed using the CC1 retrieval system [cat. no. 950-124; Roche Diagnostics (Shanghai) Co., Ltd.] in accordance with the manufacturer's antibody specifications and standard instrument protocols. After routine washing, sections were incubated with primary antibodies following the platform's standard operating procedures. Ready-to-use primary antibodies against pan-cytokeratin (CK) (cat. no. ZM-0063), CK5/6 (cat. no. ZM-0313), P40 (cat. no. ZM-0432) and Ki-67 (cat. no. ZM-0166) were obtained from Zhongshan Golden Bridge Biotechnology Co., Ltd. and applied without further dilution. Programmed death ligand 1 (PD-L1) expression was evaluated using the PD-L1 IHC 22C3 pharmDx kit (clone 22C3; cat. no. SK006; Dako; Agilent Technologies, Inc.). The linker-based detection components (HQ-linker and HRP-conjugated multimer) and chromogenic detection reagents were integrated within the OptiView DAB IHC Detection System [cat. no. 760-700; Roche Diagnostics (Shanghai) Co., Ltd.]. This ready-to-use kit was designed for the Ventana BenchMark ULTRA automated staining platform, and all kit reagents were applied undiluted. Specific antigen signals were visualized using the DAB chromogen supplied in this kit. Nuclei were lightly counterstained with hematoxylin.

Figure 1. Clinical course of the lower-lip lesion before and after CT-guided ^{125}I seed brachytherapy. (A) The tumor was cauliflower-shaped before seed implantation, with visible surface hemorrhage and necrosis. (B) At 2 weeks after seed implantation, the tumor size noticeably decreased. (C) At 1 month after seed implantation, the tumor further shrank and necrotic tissue appeared. (D) At 2 months after seed implantation, the tumor nearly showed a marked clinical regression, leaving scabs and tumorous protrusions. (E) At 6 months after seed implantation, the tumor showed a marked clinical regression and the area exhibited scar healing. (F) At 2 years after seed implantation, the area was fully healed with complete scar formation.

Positive and negative controls were rigorously included in each staining run. Archived human tissue specimens with confirmed positive target-protein expression were used as positive controls. For negative controls, primary antibodies were replaced with isotype-matched non-immune IgG at equivalent concentration, with all other experimental conditions unchanged. All control slides were processed in parallel with study sections in every staining batch. IHC staining was positive for CK5/6, CK and P40, with a Ki-67 proliferation index of 40%; P53 and P16 were negative, and PD-L1 expression was undetectable in tumor cells (Fig. 3). Based on the radiological, serological and histopathological findings, the patient was diagnosed with moderately differentiated lip squamous cell carcinoma with right cervical lymph node metastasis, staged as cT3N2bM0 (stage IVA) according to the American Joint Committee on Cancer staging system (17).

Therapeutic intervention. In September 2018, the patient underwent ^{125}I seed brachytherapy for treatment of the primary lip squamous cell carcinoma. Preoperative CT-guided target delineation was performed rigorously: The gross tumor volume (GTV) was defined based on the visible tumor on CT images, and the clinical target volume was generated by expanding the GTV by 3-5 mm to cover potential microscopic infiltration. The prescribed dose was 140 Gy. This was consistent with the head and neck squamous cell carcinoma brachytherapy guidelines of the American Brachytherapy Society and the American College of Radiology, which recommend 120-160 Gy, as well as with our institutional experience (18,19). Patient positioning was optimized according to tumor location and preoperative CT localization was performed. Local anesthesia was administered, and needle trajectories and angles were precisely adjusted. A total of five needle channels were established in strict accordance with the preoperative plan (Fig. 2B). Model 6711 sealed ^{125}I seeds (Shanghai Syncor Medicine Corp., Ltd.) were used, with a single-seed activity of 0.6 mCi and a physical half-life of 59.4 days. After the needle tips reached the distal tumor margin, the needles were retracted at equal intervals for seed deposition. A total of 43 seeds were implanted to deliver the prescribed 140 Gy. Immediate postprocedural CT confirmed homogeneous seed distribution without leakage or aggregation (Fig. 2C). For perioperative pain control, the patient received a single subcutaneous dose of morphine (5 mg) ~30 min preoperatively and intravenous flurbiprofen axetil (50 mg) during the procedure; the postoperative visual analogue scale pain score decreased to 2-3/10.

In November 2018, the patient underwent CT-guided three-dimensional (3D) template-assisted ^{125}I seed brachytherapy for the metastatic cervical lymph nodes, following the same target delineation principles. A total of 35 ^{125}I seeds (each with an activity of 0.56 mCi) were implanted to deliver a prescription dose of 140 Gy.

No serious procedure-related complications occurred during treatment or follow-up. The patient developed only mild local swelling on the first postoperative day, which resolved spontaneously within 3 days. No bleeding, surgical site infection, skin ulceration, ORN or xerostomia was observed during long-term follow-up.

Follow-up and outcomes. After radioactive ^{125}I seed implantation, X-ray imaging revealed well-distributed seeds (Fig. 2D). Postoperative dosimetric parameters were as follows [Dx represents the minimum dose covering x% of the planning target volume (PTV) and Vx indicates the percentage of the PTV receiving at least x% of the prescribed dose]: D90, 141.7 Gy; D100, 37.3 Gy; V90, 99.5%; V100, 98.2%; and

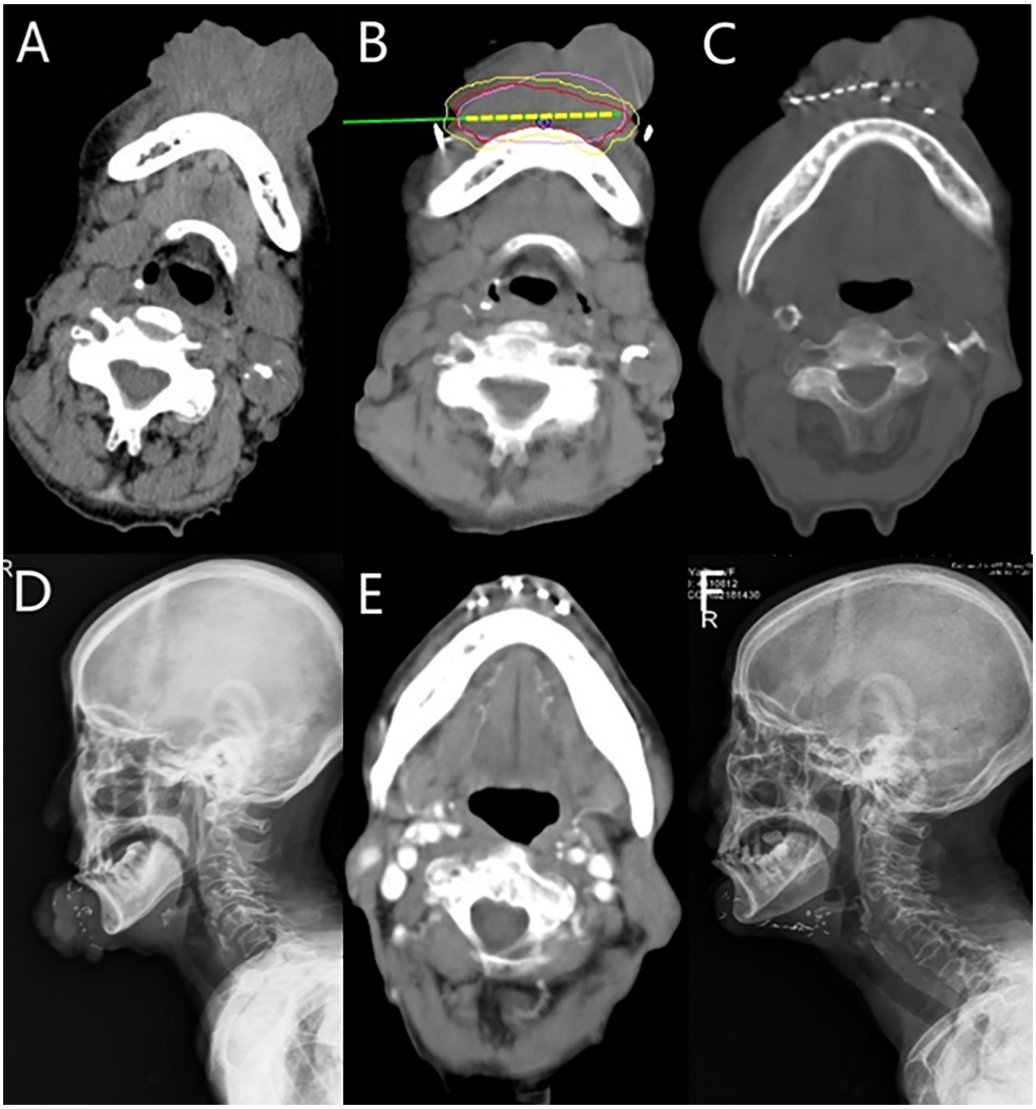

Figure 2. (A) Pre-implantation CT scan showing a space-occupying lesion on the lower lip, measuring 4.0 x 7.0 cm. (B) Schematic diagram illustrating the treatment plan and design before seed implantation. (C) CT image taken immediately after seed implantation. (D) X-ray image 2 days after seed implantation showing well-distributed seeds at the tumor base. (E) CT scan 2 months after surgery revealing significant tumor shrinkage and seed accumulation. (F) X-ray image 2 days after seed implantation in metastatic neck lymph nodes, showing even seed distribution. CT, computed tomography.

V150, 75.8% (Fig. 4A). These parameters, particularly the D90 exceeding 140 Gy, suggested adequate dosimetric coverage for tumor control. The tumor size substantially decreased at 2 weeks (Fig. 1B). The tumor shrank further at 1 month, with the appearance of necrotic tissue (Fig. 1C). Further shrinkage was evident at 2 months, with only scabbing and a residual tumorous protrusion (Fig. 1D). CT imaging revealed marked tumor reduction and ^{125}I seed accumulation (Fig. 2E).

After radioactive ^{125}I seed implantation for cervical lymph node metastasis, X-ray imaging revealed homogeneous seed distribution in metastatic neck lymph nodes (Fig. 2F). The postoperative target volumes were as follows: D90, 143.8 Gy; D100, 99.4 Gy; V90, 96.2%; V100, 94.6%; V150, 74.1% (Fig. 4B). Comprehensive assessment was performed every 2-3 months and indicated gradual reduction of the lesion. Both the lip tumor and the cervical lymph node metastases displayed a marked clinical regression after 6 months (Fig. 1E). The patient experienced an obvious improvement in mouth opening, swallowing and chewing functions, and was capable of normal oral intake. No adverse effects, including xerostomia and hyposalivation, and ORN, were observed.

At 2 years after the treatment, the lower-lip lesion had healed completely with cicatricial tissue, leaving a smooth and flat scar surface (Fig. 1F). The patient's Karnofsky performance status (20) score was 90. To date (last follow-up: December 2025), the patient remains alive, with overall survival exceeding 7 years. The case timeline is summarized in Fig. 5.

Discussion

Managing locally advanced lip squamous cell carcinoma in elderly patients with multiple comorbidities remains a formidable clinical challenge. In the present case, an 80-year-old woman with Alzheimer's disease and stage IVA (cT3N2bM0) lip squamous cell carcinoma was deemed ineligible for curative surgery and definitive EBRT following multidisciplinary consensus. Accordingly, CT-guided 3D

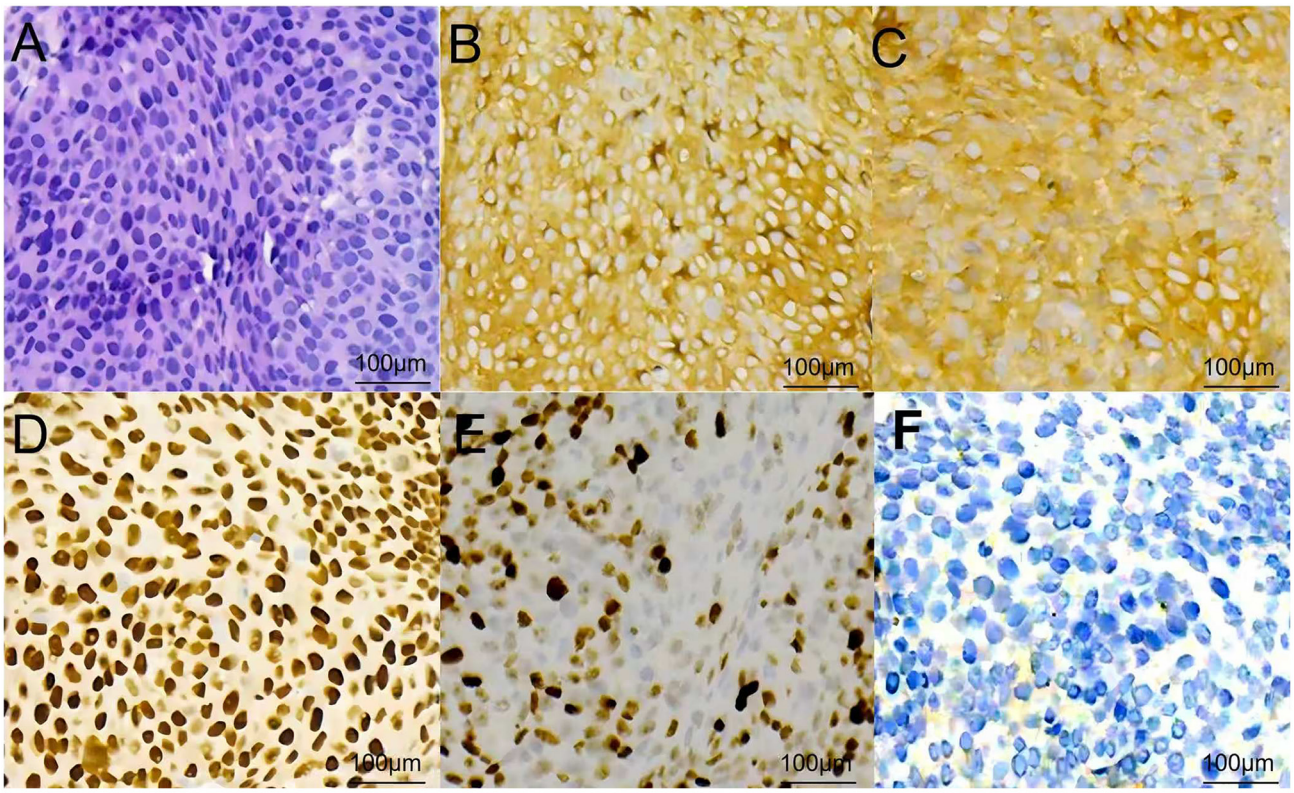

Figure 3. Histopathological analysis of lip squamous cell carcinoma (scale bars, 100 μm; magnification, x20). (A) Hematoxylin and eosin staining showing infiltrative nests of atypical squamous epithelial cells with keratin pearls and distinct intercellular bridges. (B) Immunohistochemical staining for CK displays diffuse cytoplasmic positivity in tumor cells. (C) The universal squamous epithelial marker CK5/6 is extensively expressed in the cytoplasm of tumor cells. (D) P40 (squamous-specific nuclear marker) exhibits strong diffuse nuclear positivity in almost all tumor cells. (E) The Ki-67 index reaches ~40%, reflecting moderate tumor cell proliferation. (F) No membranous PD-L1 positivity is observed in tumor cells (tumor proportion score <1%). CK, cytokeratin; PD-L1, programmed cell death ligand 1.

template-assisted ^{125}I seed brachytherapy was implemented, shifting the therapeutic goal from complete radiologic response to durable long-term tumor control with maximal preservation of organ function.

Our institution has extensive experience with CT-guided 3D template-assisted radioactive ^{125}I seed implantation for refractory solid malignancies (18,19,21,22), with proven efficacy and safety in lung cancer, liver cancer and osseous metastases (23-25). This minimally invasive technique has also yielded promising outcomes in recurrent and metastatic head and neck malignancies (12-14,26). Building on this institutional foundation, the entire procedural workflow was systematically optimized, including preoperative planning, 3D template fabrication, intraoperative guidance and postoperative dosimetric verification, with individualized adjustments based on the anatomy and clinical status of the patient.

This case yields three pivotal clinical insights. First, it validates a patient-centric evaluation paradigm for cognitively impaired elderly patients who cannot perceive or articulate subtle symptoms. For this vulnerable population, treatment efficacy should be assessed comprehensively through sustained tumor control and preservation of physiological functions, including oral intake, verbal communication and facial structural integrity. Second, 3D-printed template technology enables precision dose sculpting comparable to surgery, achieving highly conformal target coverage while effectively sparing adjacent key structures. This level of accuracy is difficult to achieve with conventional EBRT. Third, the patient's unprecedented 7-year survival challenges the traditional perception of interstitial brachytherapy as merely palliative, thereby confirming its potential curative value in carefully selected patients with unresectable advanced lip squamous cell carcinoma.

Comparison with the existing data contextualizes the remarkable outcome observed in this case. Tian *et al* (14) reported a series of oral squamous cell carcinomas treated with ultrasound-guided radioactive ^{125}I seed implantation, with a median follow-up of 15 months. Li *et al* (12) evaluated image-guided radioactive ^{125}I seed implantation as salvage therapy in 13 patients with recurrent soft-tissue sarcomas after prior surgery and radiotherapy, achieving a local control rate of 69.2% and a median overall survival of 17 months. Zhang *et al* (13) reported a median overall survival of 15 months in a larger cohort of 132 patients with inoperable head and neck cancers. Collectively, these studies confirm that ^{125}I seed brachytherapy can provide substantial tumor control and survival benefit even in advanced or recurrent disease. In the present study, the patient's sustained remission beyond 84 months extends the observed survival horizon for this modality. This outcome suggests that the therapeutic potential of ^{125}I seed brachytherapy may substantially exceed the median survival benchmarks reported previously in appropriately selected patients who achieve a favorable response.

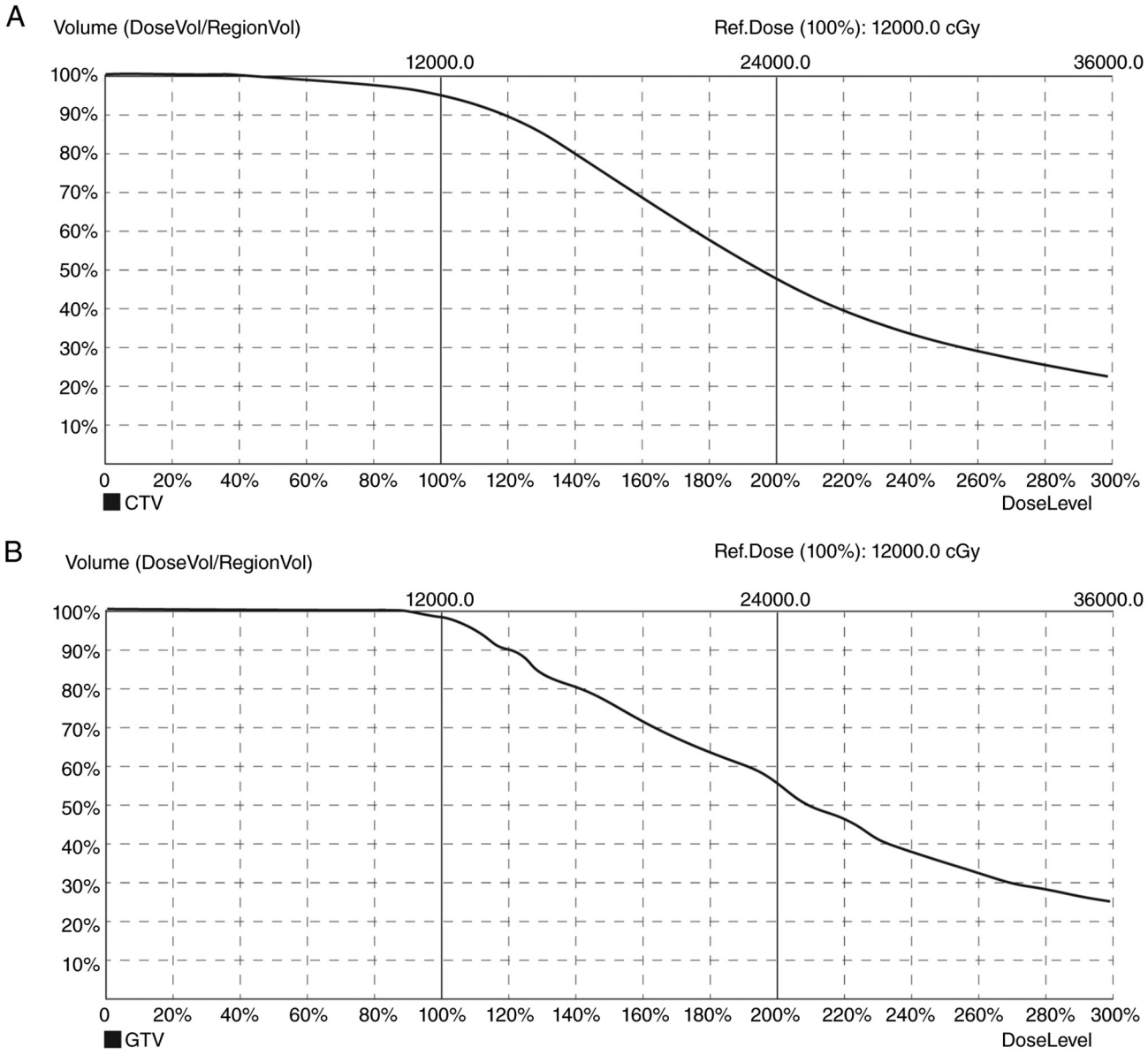

Figure 4. (A) DVH plots after radioactive ^{125}I seed implantation for lip tumor. (B) DVH plots after radioactive ^{125}I seed implantation for cervical lymph node metastasis. DVH, dose-volume histogram.

This study had several limitations. The patient could not cooperate with regular CT or magnetic resonance imaging examinations owing to progressive cognitive deterioration from advanced Alzheimer's disease, precluding standardized serial radiological follow-up and objective imaging-based response assessment. Nonetheless, sustained clinical remission, complete wound healing, intact oral and facial function, and asymptomatic survival for 7 years constitute robust patient-centric evidence of long-term efficacy and safety. Mechanistically, the continuous low-dose-rate gamma radiation emitted by ^{125}I seeds induces persistent DNA damage and irreversible tumor cell apoptosis. Interstitial implantation precisely confines high-dose radiation to the target lesion while minimizing peripheral exposure (27,28). For locally invasive head and neck squamous cell carcinoma with cervical lymph node metastases, the American Brachytherapy Society (29) and American College of Radiology (30) brachytherapy guidelines recommend a prescription dose of 120-160 Gy. In the present study, 140 Gy was chosen as the target prescription dose for two key reasons. First, the primary lip tumor invaded the underlying musculature to a maximum depth of 2.5 cm, with multiple metastatic nodes in levels II-III of the right neck. These features necessitated a relatively high radiation dose to eradicate microscopic disease. Second, the present single-center retrospective data showed that 3D template-guided implantation with a 140-Gy prescription dose consistently yielded a D90 of ≥140 Gy for both primary and metastatic lesions. This ensures full clinical target volume coverage while limiting high-dose radiation to adjacent normal lip and oral mucosal tissues. In the present case, the D90 values for the primary tumor and cervical nodes were 141.7 and 143.8 Gy, respectively-both exceeding the prescribed threshold. These dosimetric results provide strong assurance for achieving durable local tumor control and sustained clinical remission. A D90 exceeding 140 Gy provides sufficient dosimetric assurance

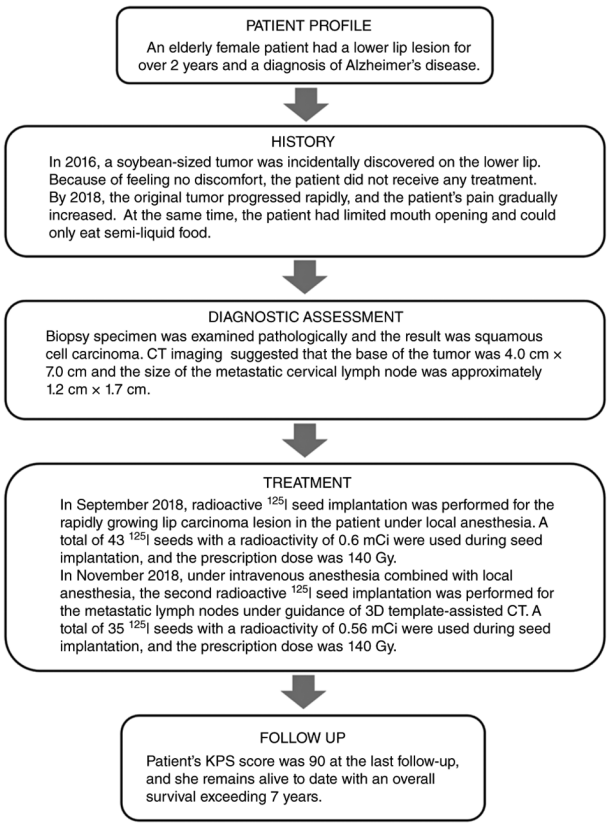

Figure 5. Timeline summarizing the patient's profile, history, examination, routine investigations, ultrasonography, contrast-enhanced computed tomography, diagnosis, treatment and follow-up. KPS, Karnofsky performance status.

for radical tumor eradication, and 3D-printed templates ensure millimeter-scale accuracy in needle placement, thus effectively eliminating low-dose cold spots and reducing radiation-related complications (31,32).

In conclusion, CT-guided 3D template-assisted ^{125}I seed brachytherapy represents a highly efficacious, minimally invasive and function-preserving therapeutic alternative for patients with locally advanced lip squamous cell carcinoma who are unsuitable for conventional curative treatment. In the present case, this individualized approach achieved durable tumor control while preserving quality of life in an elderly patient with cognitive impairment. Larger prospective trials are warranted to refine patient selection criteria, standardize treatment procedures and optimize dosimetric parameters for broader clinical adoption of this approach.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

GZ, SY and JZ conceived and designed the study. GZ, SY, XZ, FX, LX and QW collected and analyzed the clinical, imaging and pathological data. GZ, SY and XZ interpreted the data and drafted the manuscript. JZ and SL supervised the study. SL performed radiological image evaluation, sorted imaging data, participated in dosimetric analysis and organized all figure preparation. SL and JZ critically revised the manuscript for important intellectual content. GZ, XZ and SY contributed to manuscript review, revision and English language polishing. GZ and JZ confirmed the authenticity of all raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Affiliated Zhongshan Hospital of Dalian University (approval no. 2022111).

Patient consent for publication

Written informed consent was obtained from the patient's son for publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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