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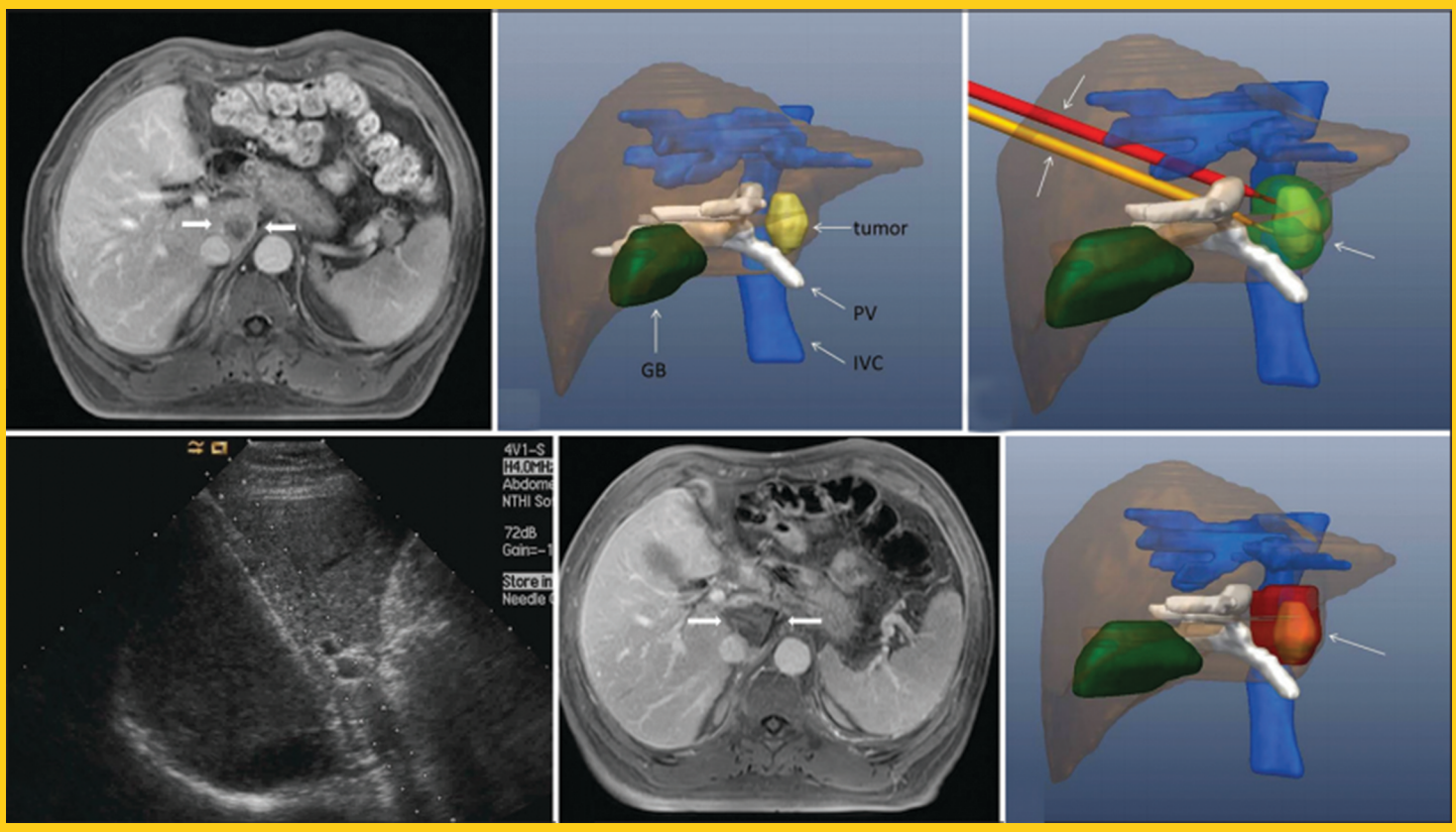

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Original Article

Image fusion technique for target volume delineation in ^{125}I seed implant brachytherapy for parotid gland cancers

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ABSTRACT

Purpose: Variability in volume delineation is a possible error source in brachytherapy. This study assessed the interobserver variations in clinical target volume (CTV) delineation in postoperative adjuvant ^{125}I seed implant brachytherapy after parotid gland cancer surgical resection and evaluated the image fusion technique for target volume delineation.

Material and Methods: Five radiation oncologists delineated gross tumor volume (GTV) and CTV in 20 patients using conventional delineation and image fusion methods. The consistency in target volume delineation was determined on the basis of differences between the oncologists. Variability was determined using Kendall's *W*-test, the mean conformity index (CI), the mean distance to conformity (MDC), and the center of gravity distance (CGD).

Results: There were significant variations in the delineated target volumes among radiation oncologists, but the CTV consistency was significantly enhanced using the image fusion technique, based on Kendall's W, mean CI, average MDC, and average CGD, which were 0.752, 0.41, 2.75, and 4.997, respectively, using the conventional method, and 0.987, 0.86, 0.55, and 1.27, respectively, using the image fusion method.

Conclusions: The interobserver variation in the delineation of the postoperative parotid target volume is large, but it can be considerably decreased using image fusion technology, which resulted in a noticeable improvement in the delineation precision of the target volume for parotid gland cancer. Thus, this technology can enhance the efficacy of ^{125}I seed implant brachytherapy and decrease any adverse effects induced by errors in target delineation.

KEY WORDS: Image fusion, parotid gland cancer, target volume comparison, target volume delineation

INTRODUCTION

Surgical resection is currently the mainstay treatment modality for parotid gland malignancies.[1] External beam radiotherapy is usually applied as a single adjuvant treatment to decrease the risk of local recurrence after surgical resection.[2,3] As an alternative, interstitial brachytherapy is capable of delivering high-conformity radiation doses to target volumes, and it provides a high local control rate with few side effects.[4,5] ^{125}I seed implant brachytherapy involves permanent implantation of radioactive seeds of ^{125}I inside the initial tumor and adjacent suspicious tissues, usually used as a postoperative adjuvant treatment.[6-8] According to the experience gained in our center, for patients with relatively low-grade or non-advanced cancer, whole parotid gland radiation therapy is excessive and inappropriate, and may induce excessive radiation toxicity to adjacent organs and normal parotid tissue.

The clinical efficacy of brachytherapy directly depends on delineation accuracy of the target volume, which is also the most time-consuming step in preparing the radiotherapy plan.[9] However, variability in volume delineation is recognized as a critical error source in radiotherapy.[10] A previous study indicated that a de-normalized volume delineation could lead to a 20% higher risk of recurrence after radiotherapy for head and neck cancer.[11] Particularly, there could be substantial heterogeneity in target volume delineation

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across various radiation oncologists. According to Major *et al.*,[12] significant interobserver variability in delineations of the lumpectomy cavity and target volume was observed among radiation oncologists in accelerated partial breast irradiation using multi-catheter brachytherapy. Despite these shortcomings, there is no gold standard to validate the accuracy of target volume delineation after parotid gland resection in brachytherapy. No study has reported the techniques for contouring the target volume in postoperative adjuvant ^{125}I seed brachytherapy for malignant parotid gland tumors.

In postoperative adjuvant brachytherapy for parotid gland carcinoma, because the tumor has already been removed, the original structure of the gland has changed and the postoperative computerized tomography (CT) does not show a clear outline of the tumor bed. Additionally, as the surrounding tissue is displaced after surgery, the target area's visualization accuracy was affected. The target area can only be determined by referring to the location and range of the preoperative CT scans and the boundary of postoperative seroma formation. Additionally, subjective differences in understanding the anatomical structure, interpretation of the CT scan, and determination of the target area between doctors can cause differences in the delineation of the postoperative target area of parotid cancer. Thus, determining the tumor site and borders accurately on postoperative CT images is an inevitable problem. This study evaluates the variation in target volume delineation between various doctors for adjuvant ^{125}I seed implant brachytherapy after parotid cancer surgery. Additionally, a preoperative and postoperative CT image fusion technique was designed and its efficiency for target volume delineation was explored as a more objective and accurate method for delineation in brachytherapy.

MATERIAL AND METHODS

Patients

The inclusion criteria were (1) superficial parotid malignant tumor at clinical stage T1–T3, (2) all patients underwent extensive local excision and had positive surgical margins on final surgical pathology, (3) preoperative CT scan indicating a clear tumor boundary, (4) absence of clinical lymph node metastasis, and (5) no history of previous surgery or radiotherapy.

Based on the inclusion criteria, 20 patients with parotid carcinoma who underwent surgical resection and postoperative adjuvant therapy using ^{125}I radioactive seed implantation at Peking University Stomatology Hospital were selected. The closely adherent facial nerve trunks or branches were stripped from the tumor mass during operation. All patients did not undergo neck dissection because there was no clinical or radiographic evidence of associated nodal metastasis in the neck. Eight of these patients were male, and twelve were female, and their ages ranged from 13 to 67 years (median, 41.5 years). The histological types of the 20 patients included mucoepidermoid carcinoma (10 cases), acinar cell carcinoma (5 cases), epithelial myoepithelial carcinoma (3 cases), and secretory carcinoma of the salivary glands (2 cases). The clinical staging of the tumors according to the American Joint Committee on Cancer (AJCC) staging criteria (eighth edition) is indicated in Table 1.

All patient images were retrospectively included based on the data collection and study protocol approved by the Ethics Committee of the Peking University Stomatology Hospital, and all participants provided written informed consent before registration.

Conventional method of target volume delineation

The postoperative CT data of 20 patients were brought into the brachytherapy treatment planning system (BTPS; Beijing Astro Technology Ltd. Co., Beijing, China). Five experienced radiation oncologists were invited to independently delineate the gross tumor volume (GTV) on the postoperative CT images by referring to the preoperative CT images. In correspondence with previous research conducted by our research group,[13,14] the planning target volume included a 1 cm margin around the preoperative GTV. The GTV thus determined was defined as GTV1. Accounting for the possible presence of microscopic disease, a 1 cm margin was added to the GTV, which was defined as clinical target volume 1 (CTV1). Later, the CTVs were manually revised using a nonisotropic geometrical extension by adding a 1 cm margin around the GTVs according to the anatomical barriers (e.g., external auditory canal and skull). Data from 100 CTVs from 20 patients were generated by the 5 radiation oncologists and allocated to Group 1.

Delineation with the image fusion technique

For target volume delineation with the image fusion technique, the image fusion tools of Materialize Mimics version 19.0 software (Materialize, Leuven, Belgium) were used to align the preoperative image against the postoperative image. The procedure comprises the following steps: (a) the region of interest, manually defined to cover the parotid and surrounding anatomic structures, (b) postoperative CT images were co-registered to preoperative CT images automatically through rigid registration of the bony anatomy, and (c) adjustments were made manually by visual inspection if required. The acquired digital imaging and communications in medicine (DICOM) images were exported to BTPS after visual comparison. The fusion image has preoperative tumor data and postoperative skin data. The pre- and postoperative CT data of the same 20 patients were imported into BTPS. The five radiation oncologists contoured GTV on the fused images and defined them as GTV2. As explained earlier, CTV2 was obtained by the automatic addition of a 1 cm margin to GTV2 in BTPS, and CTV2 was later manually revised based on the anatomical barriers. The workflow for the procedures is shown in Figure 1. The final values from 100 CTVs (of the 20 included patients) were allocated to Group 2.

Table 1: Clinical stages of the patients (*N*=20)

Patients	Diagnosis	Tumor size (cm)	T	Stage
1	Acinar cell carcinoma	1.5×1.9×1.7	T1	I
2	Mucoepidermoid carcinoma (M)	2.6×1.6×1.4	T2	II
3	Mucoepidermoid carcinoma (H)	3.6×3.3×2.7	T2	II
4	Acinar cell carcinoma	3.5×3.2×3.1	T2	II
5	Mucoepidermoid carcinoma (H)	1.5×1.0×1.0	T1	I
6	Epithelial myoepithelial carcinoma	2.4×1.9×2.9	T2	II
7	Mucoepidermoid carcinoma (H)	2.1×1.3×1.5	T2	II
8	Mucoepidermoid carcinoma (L)	2.0×1.9×2.1	T2	II
9	Mucoepidermoid carcinoma (H)	1.8×1.7×1.5	T1	I
10	Epithelial myoepithelial carcinoma	1.5×1.2×2.3	T2	II
11	Epithelial myoepithelial carcinoma	2.9×2.2×2.7	T2	II
12	Mucoepidermoid carcinoma (H)	2.3×1.9×2.3	T2	II
13	Mucoepidermoid carcinoma (L)	3.4×2.0×2.9	T2	II
14	Mucoepidermoid carcinoma (H)	2.3×1.8×1.4	T2	II
15	Acinar cell carcinoma	1.8×1.5×1.5	T1	I
16	Secretory carcinoma of salivary glands	4.3×3.8×4.5	T3	III
17	Secretory carcinoma of salivary glands	3.8×2.4×3.7	T2	II
18	Acinar cell carcinoma	1.6×1.1×1.5	T1	I
19	Acinar cell carcinoma	2.2×1.5×1.5	T2	II
20	Mucoepidermoid carcinoma (H)	2.8×4.3×4.5	T3	III

H, high grade; L, low grade; M, medium grade

Preplanning procedure

According to the standard clinical protocol, all the five radiation oncologists designed all implantation plans using BTPS. The matched peripheral dose was defined as 110 Gy for CTV, and implantation of ^{125}I seeds in the target volume along the needle paths at an activity level of 0.6 mCi was simulated.

Statistical analysis

Kendall's *W*-test was used to evaluate the differences in the CTVs that the five radiation oncologists sketched. The *P* values < 0.05 were considered to indicate statistical significance.

The conformity index (CI), defined as the ratio between common CTVs and total encompassing CTVs of five contours, was used to quantify the similarity of target delineations.[15,16] The CI was proposed by Kouwenhoven *et al.*,[17] which was determined independently by the number of delineated volumes or observers. A CI value of 100% shows that all target volumes were utterly consistent, and a CI value of 0% shows that all target volumes were utterly inconsistent.

To quantify the spatial relationship in the 3D space between various target volumes, the concepts of center of gravity distance (CGD) and mean distance to conformity (MDC) were used. CGD is defined as the distance between the contour centers of two target volumes,[18] and MDC, as defined by Yena *et al.*,[19] is considered the average distance that each point in the target contour needs to move to match the position of the corresponding point in another contour. In the case of MDC and CGD, lower values show higher correspondence between the compared volumes. MDC and CGD were determined using BTPS and evaluated the degree of difference between CTVs. The differences in the MDC and CGD values between two radiation oncologists were calculated, and the mean MDC and CGD values were also calculated.

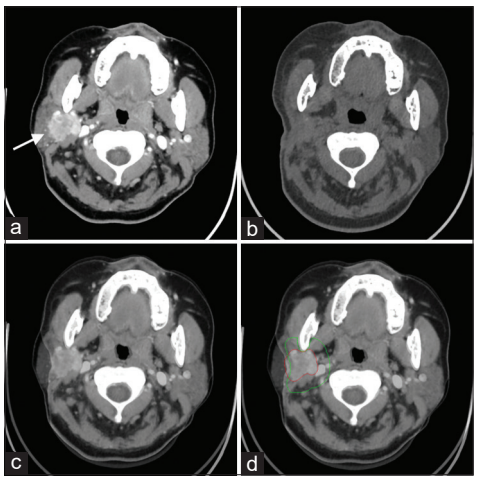

Figure 1: Delineation with the image fusion technique. (a) Preoperative CT images, the site of the tumor and the borders can be determined accurately. (b) Postoperative CT images, the tumor has been removed already, the original structure of the gland has changed and postoperative CT does not depict a clear outline of the tumor bed. (c) Align the preoperative image against the postoperative image via rigid registration of the bony anatomy. (d) One of radiation oncologists contoured GTV on the fused images, then CTV was obtained by automatically adding a 1 cm margin around the GTV. CTV was later manually revised based on the anatomical barriers

Statistical analysis was conducted using the Statistical Package for the Social Sciences (IBM SPSS, version 22.0).

RESULTS

In Group 1, 100 target volumes were delineated on the postoperative CT images by the five radiation oncologists. The variations in CTV1 ranged from 6.3 cm^3 to 56.1 cm^3 for an individual patient. Additionally, the minimum difference

between the CTV values in the same patient was 0.2 cm^3, whereas the maximum difference was 20.5 cm^3.

In Group 2, the target volumes delineated were based on the changes in the contour of the preoperative tumors and the postoperative surrounding tissue. The CTV2 variations in the same patient, based on the delineated volumes by the five radiation oncologists, ranged from 3.8 cm^3 to 47.6 cm^3. In the same patient, the minimum variation in CTV2 between the five radiation oncologists was 0 cm^3, and the maximum variation was 6.4 cm^3.

Kendall's coefficient and CI for the five radiation oncologists in Group 1 was 0.752 and 41%, respectively; in Group 2, these were significantly enhanced, at 0.987 and 86%, respectively. Furthermore, Kendall's *W*-test indicated that volumes in Group 1 were consistent ($P = 0.01$), but the consistency level was lower than that in Group 2. Analysis of the CI values corresponding to the CTVs for the five radiation oncologists in each patient showed that the overlapping parts only accounted for 41% of the total volume, on average, in Group 1 (mean CI = 41%), whereas the consistency in Group 2 was significantly improved (mean CI = 86%) [Table 2].

The MDC and CGD values determined by the five radiation oncologists are indicated in Table 3. Comparison of intergroup data indicated a highly significant reduction in MDC and CGD in Group 2 compared to Group 1. When MDC and CGD were combined with CI [Table 2], the findings showed that the target volume of the same patient, as determined by various radiation oncologists in Group 1, had a large deviation in the 3D space, and that the application of image fusion technology effectively decreased this deviation.

The five radiation oncologists designed the implantation plan, and the mean and standard deviations (STDs) of the ^{125}I seed number for the 20 patients are indicated in Table 4. Group 2 STD was significantly lower than that of Group 1 [Table 4].

Table 2: Comparison of Kendall's *W* test and mean CI in Groups 1 and 2

	Group 1	Group 2
mean CI	0.41	0.86
Kendall's *W* (volume)	*W*=0.752 (*P*=0.01)	*W*=0.987 (*P*=0.00)
Kendall's *W* (layer)	*W*=0.838 (*P*=0.01)	*W*=0.973 (*P*=0.00)

Table 3: MDC and CGD values indicating variation in CTV among five radiation oncologists

Patients	MDC		CGD	
	Group 1	Group 2	Group 1	Group 2
1	3.68	0.43	5.82	0.36
2	1.66	0.29	3.45	1.02
3	2.27	0.44	4.66	1.32
4	2.27	0.11	3.11	0.46
5	3.31	0.15	6.75	0.47
6	1.42	0.39	3.08	0.62
7	3.30	0.95	6.68	2.18
8	3.03	0.70	4.25	1.48
9	2.89	0.25	5.18	0.68
10	2.13	0.31	5.10	0.47
11	1.13	0.06	1.54	0.38
12	3.70	1.19	7.73	2.68
13	7.38	0.74	3.15	1.72
14	3.45	0.72	9.00	0.39
15	3.59	0.29	8.15	0.69
16	1.86	1.50	3.55	4.95
17	2.46	0.89	4.62	2.04
18	1.88	0.65	5.15	1.84
19	1.22	0.53	2.91	0.73
20	2.43	0.36	6.07	0.94
mean	2.75	0.55	4.997	1.27

MDC is the average distance required for each point in the target contour to move to match position of the corresponding point in the reference contour. CGD is the distance between the contour centers of two target volumes

DISCUSSION

This study investigated the inter-assessor variation in target volume delineation for adjuvant ^{125}I seed implant brachytherapy after parotid cancer surgery. Additionally, the effectiveness of a pre- and postoperative CT image fusion technique was also evaluated in terms of improving the accuracy of delineation.

The accuracy of target delineation for ^{125}I radioactive seed implantation after parotid cancer surgery ultimately affects the seed implantation plan, including the number and seed distribution. In this study, the number of seeds for implantation in the same patient, as determined by various doctors, significantly varied, and the STD for 20 included patients is 3.59 on an average. However, after the application of the image fusion technique, the STD was significantly decreased to 0.91. Additionally, these findings showed that variations in the target area outlined by various doctors for the same patient decreased significantly using the image fusion technique, based on the MDC and CGD values, which are considered as important indicators for quantitating mismatch in the shape between the two contours.[18,20] Thus, the application of image fusion technology can decrease the deviation in the 3D target area outlined by various doctors through a significant decrease in the deviation in volume and 3D space of various radiotherapy targets, and thereby affecting the final number and distribution of particle implantation. Overall, the conformity of the target volumes increased from 41%, with the traditional delineation method, to 86%, with the image fusion technique.

In adjuvant radiotherapy for other types of malignant masses like breast cancer, the tumor bed was determined based on tumor bed clips and surgery-related seroma,[21] but in daily clinical practice, most parotid masses are benign and operated before obtaining the final histological diagnosis. As a result, the placement of silver clips was not accepted as a routine intraoperative procedure. Additionally, parotid show fewer postoperative seroma and tissue remodeling without obvious tumor margins. For these reasons, preoperative

Table 4: Seed implantation

Patients	A		B		C		D		E	
	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2
1	15	16	10	16	11	17	21	16	16	17
2	18	15	20	16	17	15	19	15	22	16
3	19	19	21	19	14	18	18	19	24	17
4	21	18	22	17	18	18	18	18	19	17
5	17	18	25	17	16	19	19	19	19	20
6	25	24	23	23	26	25	18	25	23	23
7	19	17	28	18	20	15	20	19	27	18
8	19	19	27	20	16	19	26	20	25	19
9	23	15	19	15	20	16	20	15	25	16
10	26	25	32	23	27	22	23	23	23	24
11	34	26	29	26	27	26	26	26	34	26
12	21	21	26	23	38	22	34	24	29	23
13	37	33	43	33	38	35	28	32	42	34
14	36	28	37	30	35	28	29	27	26	29
15	37	25	29	23	35	25	33	26	31	23
16	48	42	43	41	50	42	48	41	49	43
17	34	36	38	35	45	35	36	34	42	37
18	37	33	41	34	39	34	42	31	41	33
19	39	39	39	37	39	38	36	37	39	38
20	50	38	51	39	52	40	54	38	58	40
STD	10.62	8.71	10.18	8.53	12.55	8.89	10.59	7.97	11.13	8.86

imaging is vital to guide tumor margin determination in postoperative adjuvant brachytherapy for parotid cancer. In our center, it was considered that the clinical target volume (CTV) was determined on the basis of preoperative CT using a uniform 1 cm expansion from the scope of tumor invasion. However, the lack of a widely accepted official gold standard in postoperative adjuvant radiotherapy could be a major limitation.

Several studies have proved that a significant interobserver variation exists in the sketching of the target volume in postoperative adjuvant radiotherapy.[22-24] Nevertheless, studies on the interobserver variation in post-parotidectomy radiotherapy are few due to the rare incidence of parotid gland tumors. Similarly, Mukesh *et al.*[25] reported an increase in conformity from 30% to 54% for segmented CTVs delineated by four oncologists for five patients who underwent postoperative radiotherapy after parotidectomy. After the target volumes were delineated, the segmentation guidelines were used to delineate the target volumes on the same CT data. The authors found that the mean conformity level (CI) of the target volumes increased from 30% to 54%., which is consistent with our finding (from 41% to 86%).

Presently, image fusion technology is widely used in planning radiotherapy regimens for oropharyngeal cancer, brain glioma, and prostate cancer.[26,27] The fusion of preoperative MRI and PET images using localized CT can significantly enhance the accuracy of radiotherapy. Furthermore, image fusion technology can also be used to evaluate postoperative recurrence after radiotherapy.[28] However, this method still has some shortcomings. For example, due to atrophy of the parotid glands after tumor resection, the delineated GTV with this method is larger than needed, especially in cases of large primary tumors for which the surrounding tissues are significantly displaced after tumor resection. Additionally, a large deviation in interobserver delineation is possible because of the formation of significant intraparotid seratoma on postoperative CT images. Besides, this study excluded the interobserver variation of organs at risk among different radiation oncologists. In the future, rigorously designed and randomized controlled trials as well as long-term follow-up investigations are needed to further confirm the applications of this image fusion technology and develop solutions for overcoming its limitations.

CONCLUSION

In conclusion, there are significant differences in the postoperative target volume for parotid gland cancers that different radiation oncologists delineate. The present findings show that the image fusion technique can effectively decrease the influence of deviations caused by human error in the delineation of the target volume and provide an effective solution for the standardization of postoperative adjuvant ^{125}I seed brachytherapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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