

# Implementation of temporal lobe contouring protocol in head and neck cancer radiotherapy planning

## A quality improvement project

Francis Ho, MD, Jeremy Tey, MD\*, David Chia, MD, Yu Yang Soon, MD, Chek Wee Tan, MDCB, Sarahatul Bahiah, MDCB, Timothy Cheo, MD, Ivan Weng Keong Tham, MD

### Abstract

Temporal lobe necrosis as result of radiation for nasopharyngeal cancer (NPC) occurs up to 28% of NPC patients. The only effective mitigation is by strict adherence to temporal lobe dose tolerances during radiotherapy planning, which in turn hinges on accurate temporal lobe delineation. We aim to improve the accuracy and to standardize temporal lobe contouring for patients receiving head and neck radiotherapy for NPC in a tertiary teaching hospital in Singapore.

The baseline data were obtained from 10 patients in the diagnostic phase and the effect of interventions were measured in 37 patients who underwent head and neck radiotherapy over a 6-month period.

We conducted the project based on the Clinical Practice Improvement Program methodology. The baseline pooled mean percentage variation in temporal lobe contouring was 39.9% (0.8%–60.2%). There was a low level of temporal lobe contouring concordance and this provided the impetus for implementation of strategies to improve the accuracy and reproducibility of temporal lobe contouring. The interventions included supervision and training of radiation therapists and residents in temporal lobe contouring, and standardization of temporal lobe contouring with a protocol and contouring atlas.

Thirty-seven patients were treated during the study period from June to November 2014. Following implementation of the first set of interventions, the pooled mean percentage variation in temporal lobe contouring decreased but was not sustained. The implementation of the second set of interventions resulted in a decrease from 39.9% (January to September 2014) to 17.3% (October to November 2014) where  $P = .004$  using  $t$  test. Weekly variation was seen throughout the study period but the decrease was sustained after standardizing and providing a contouring atlas for temporal lobe contouring.

Temporal lobe contouring can be standardized through effective implementation of a temporal lobe contouring protocol and atlas.

**Abbreviations:** CPIP = Clinical Practice Improvement Program, CT = computed tomography, DVH = dose-volume histogram, IMRT = intensity-modulated radiotherapy, MPV = mean percentage variation in temporal lobe volume, MRI = magnetic resonance imaging, NPC = nasopharyngeal cancer, OAR = organs at risk, PV = percentage variation in temporal lobe volume, RCA = root cause analysis.

**Keywords:** contouring, head and neck cancer, nasopharyngeal cancer, quality improvement project, radiotherapy, temporal lobe

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Department of Radiation Oncology, National University Cancer Institute, Singapore, Singapore.

\* Correspondence: Jeremy Tey, Department of Radiation Oncology, National University Cancer Institute, Singapore, 5 Lower Kent Ridge Road, Singapore 119074 (e-mail: Jeremy\_Tey@nuhs.edu.sg).

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## 1. Introduction

### 1.1. Background knowledge

Intensity-modulated radiotherapy (IMRT) is currently the standard treatment for patients with locally advanced nasopharyngeal cancer (NPC). IMRT is a sophisticated radiotherapy technique that allows us to deliver the prescribed radiotherapy dose to the planning target volumes in NPC, whereas reducing the dose to organs at risk (OARs) such as the temporal lobe, brainstem, and optic chiasm. Before the advent of IMRT, there was no effective way of sparing the temporal lobes of high radiation doses even with good OARs delineation as conventional radiotherapy planning systems did not possess the sophistication required. With more accurate dose delivery, accurate delineation of tumor volumes and OARs are required. Accurate delineation of OARs will ensure that the OARs will be kept within OARs constraints, minimizing the risk of acute and long-term radiotherapy side effects without compromising tumor control. Temporal lobe necrosis is a well-documented

complication of radiation for NPC affecting as many as 35% of patients who have received radiotherapy.<sup>[1]</sup> The only effective mitigation is by strict adherence to temporal lobe dose tolerances during radiotherapy planning, which in turn hinges on accurate temporal lobe delineation.

In radiation oncology, the dose-volume histogram (DVH) is one of the parameters used to assess the quality of a radiation treatment plan. The DVH in radiation oncology is a volume-based concept and allows the radiation oncologist to assess the volume of a particular OAR receiving a particular radiation dose.<sup>[2]</sup> Radiotherapy treatment protocols will typically specify the dose limit to a particular volume (in percentage or cm<sup>3</sup>) for an OAR. These include the temporal lobe and other OARs such as optic chiasm, optic nerves, brainstem, lens, cochlea, temporomandibular joints, and the parotid glands. According to Radiation Therapy Oncology Group 02-25<sup>[3]</sup> protocol for NPC treatment, the radiation doses for temporal lobe were limited to a maximum point dose of <65 Gy and 1% volume of the temporal lobe should receive <60 Gy. Other studies have found that a maximum dose of 69 Gy to no more than 0.5 cm<sup>3</sup> of the temporal lobe would limit temporal lobe injury incidence to 5% at 5 years.<sup>[4]</sup>

Regardless of the target planning dose to the temporal lobe, the ability to avoid OARs in radiotherapy planning is contingent on accurate OAR contouring. For the temporal lobes in particular, its extent and boundaries are not clearly defined in radiology textbooks. There are also no established guidelines on temporal lobe contouring in radiation oncology. Even consensus statements by cooperative groups for treatment of NPC do not include guidelines for temporal lobe contouring.<sup>[5]</sup> Our team felt that contouring accuracy is increasingly important as radiotherapy delivery becomes more targeted. Inaccuracies in OAR contouring, including temporal lobes may lead firstly to inaccuracies in treatment, secondly to overdosing of the temporal lobe. Lastly, accurate temporal lobe contouring is even more crucial when the temporal lobe is in close proximity to the nasopharyngeal tumor, especially tumors with intracranial (T4) or sphenoid sinus extension (T3). This point is well illustrated in Zeng's study where he found the incidence of temporal lobe injury to be 28% in T4 disease.<sup>[6]</sup> Accurate delineation of the temporal lobes will ensure that it will be kept within OARs constraints, minimizing the risk of acute and long-term radiotherapy side effects.

Temporal lobe necrosis is one of the dreaded toxicity of modern radiotherapy treatment. For NPC treatment, the bilateral temporal lobes may be included in radiation field treatments and are thus at risk of radiation necrosis. Our literature review showed that the incidence of temporal lobe necrosis can vary from 1% to 35%.<sup>[1,6,7]</sup>

## 2. Methods

This project was carried out as a quality improvement project within a tertiary teaching hospital in Singapore. The outcome measures were prospectively collected. Data collection for this study was approved by our local institutional ethics committee.

### 2.1. PRE Clinical Practice Improvement Program (CPIP) temporal lobe contouring pathway

Contouring in radiotherapy planning is a process whereby critical organs such as the temporal lobes are delineated on computed tomography (CT) images. This is to facilitate the calculation of radiation dose that is received by the temporal lobe after the

radiotherapy plan is completed. In general, like most radiation oncology departments, our department has a workflow whereby the organs at risk are contoured by resident physicians or radiation therapists, and counter checked by the primary radiation oncologist. Different OARs have different degrees of difficulty in their delineation. The temporal lobe is considered a difficult organ to contour for a variety of reasons. The accuracy of temporal lobe contouring may differ according to the experience and knowledge of the staff. In addition, NPCs are common cancers treated with radiation therapy and can often be managed by general radiation oncologists. This may be a problem as general radiation oncologists may have less experience in managing NPC. Head and neck OAR contouring for these radiation oncologists may also be difficult, as they have limited experience in temporal lobe contouring.

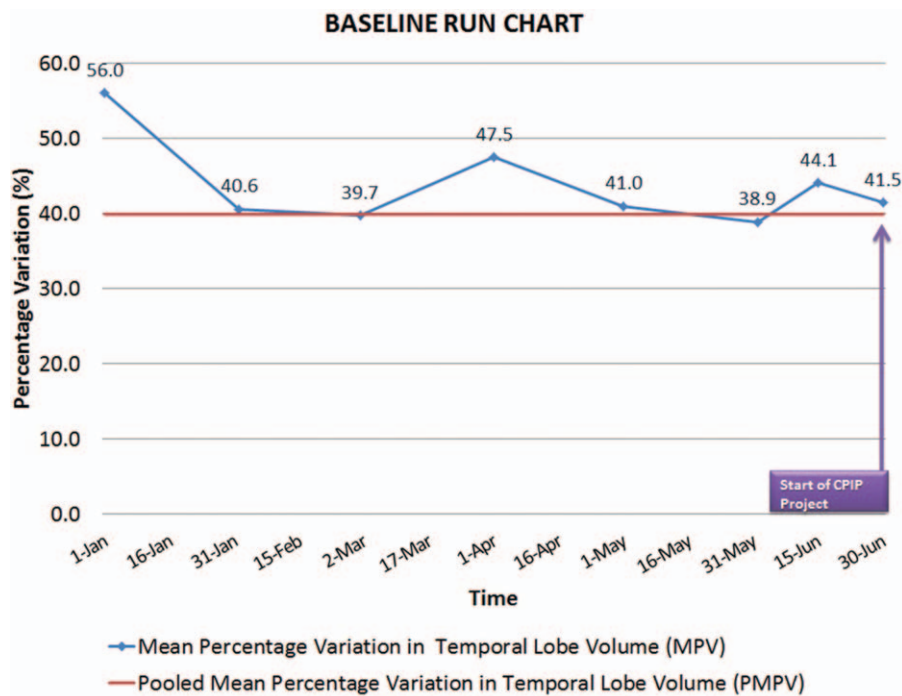
To demonstrate that there was a significant interindividual variation in the contouring of temporal lobe within the department, we did the following:

1. Owing to limited resources, we randomly selected and audited NPC patients treated in our department from January to June 2014. Two head and neck radiation oncologists retrospectively recontoured all the temporal lobes of these 10 patients treated with radiotherapy for NPCs in this time period. These temporal lobe contours were deemed the gold standard and acted as a basis for comparison.
2. We compared the variation in temporal lobe contouring in terms of absolute volume (cm<sup>3</sup>) between the temporal lobe contours by the original team versus the temporal lobe contours by the head and neck radiation oncologists.
  - Percentage variation in temporal lobe volume (PV) = volume of temporal lobe contoured by primary team/volume of temporal lobe contoured by head and neck radiation oncologist.
  - Note: the numerator and denominator were interchanged to obtain a positive number, depending on which number was greater in value.
  - Each temporal lobe contour was counted independently as a data set, and hence there were 20 PVs.
  - The mean percentage variation in temporal lobe volume (MPV) was obtained as a mean of these 10 patients' PV.
3. Results showed that MPV in temporal lobe contouring at baseline was 39.9% (0.8%–60.2%) over the period January 2014 to June 2014 for these 10 patients (Fig. 1).

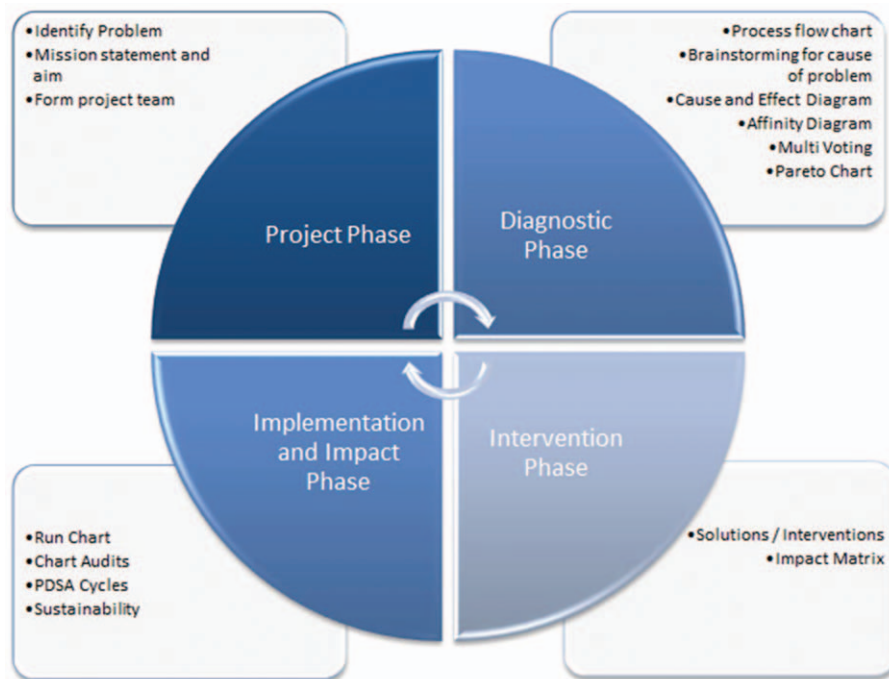
This has 2 implications. Firstly the accuracy of temporal lobe variation varied by a large extent. Secondly, because the radiation dose was calculated based on this inaccurate temporal lobe contouring, the probability of temporal lobe injury was no longer the value ascribed to it at the radiotherapy planning stage.

### 2.2. Clinical practice improvement program

We conducted the project based on the CPIP methodology<sup>[8]</sup> (Fig. 2), which applies evidenced-based medicine within a clinical improvement project. This is a methodology that has yielded significant results in implementing evidence locally in other disciplines.<sup>[9–11]</sup> Following this methodology, 2 radiation oncologists retrospectively recontoured all the temporal lobes of 10 patients treated with radiotherapy for NPCs. We compared the differences in temporal lobe contouring in terms of absolute volume (cm<sup>3</sup>). Results showed that pooled MPV in temporal lobe contouring was 39.9% (0.8%–60.2%). This provided the impetus for implementation of strategies to improve the accuracy



**Figure 1.** Run chart demonstrating baseline data. The mean percentage variation in temporal lobe volumes (MPVs) were obtained for a random audit of 10 patients treated over a 6-month period from January 2014 to June 2014. If 2 or more patients were treated in the same 2-week interval, the average of the MPVs was presented. Results showed that pooled MPV in temporal lobe contouring at baseline was 39.9%, as indicated by the red line (range 0.8%–60.2%) over the period January 2014 to June 2014 for these 10 patients.



**Figure 2.** Clinical Practice Improvement Program Process. The different phases of diagnosis and implementation in the Clinical Practice Improvement Program (CPIP) methodology, including the project phase, diagnostic phase, intervention phase, implementation and impact phase. PDSA = Plan, Do, Study, Act.

and reproducibility of temporal lobe contouring for patient receiving nasopharyngeal radiotherapy.

We followed closely the recommended template for a CPIP project:

1. Project phase:
  - Identify the mission statement and aim
  - Form project team
2. Diagnostic phase:
  - Establish the extent of the problem
  - Define interventions that will result in improvement
  - Define how improvements will be measured
3. Interventions phase:
  - Implement the interventions defined (may be >1)
4. Implementation and impact phase:
  - Measure and record the results of the intervention
  - Conduct root cause analysis (RCA) as and when results are not within expectations

**2.3. Intended improvement**

The aim of the treatment is to reduce mean percentage variation in temporal lobe contouring by 50%, from a baseline of 39.9% baseline to a target 19.9%, for patients receiving radiotherapy for NPC at the Department of Radiation Oncology at a tertiary hospital in Singapore over 6 months.

With improvement in imaging, magnetic resonance imaging (MRI) is now routinely incorporated into the diagnosis, staging, treatment planning, and surveillance for NPCs. We are now seeing increased incidence of radiologically reported temporal lobe necrosis. MRI coregistration (fusion) with our planning CT simulation scans allows us to visualize brain anatomy with better resolution. In addition, IMRT is currently the standard radiation technique for treatment of NPCs. This technique allows radiation oncologists to treat tumor to a high dose while sparing the critical OARs. Hence, the importance of accurate delineation to spare the

temporal lobe from radiation.<sup>[12]</sup> In addition, although we have been implementing the OAR constraints for temporal lobe, there has been feedback from the therapists and residents that there is no consensus within the department as to how best contour the temporal lobe.

The champion of this effort is JT and the supporters are FH, TC, DC, YYS, SB, CWT, IT.

**3. Project phase**

To arrive at our intended endpoint of reducing temporal lobe variation, we adopted the CPIP methodology. We Implemented CPIP methodology as follows:

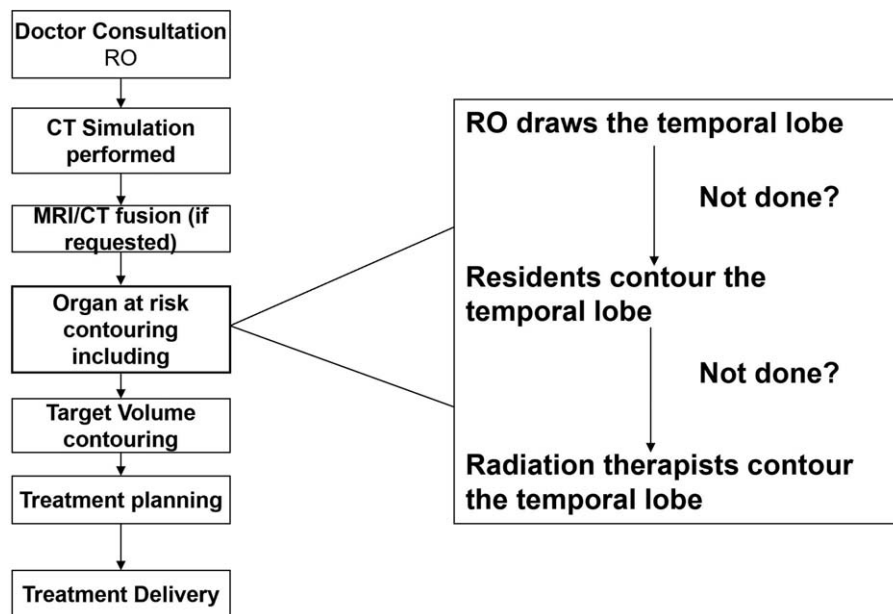
**3.1. Diagnostic phase**

Establishing the flow chart of the temporal lobe contouring process:

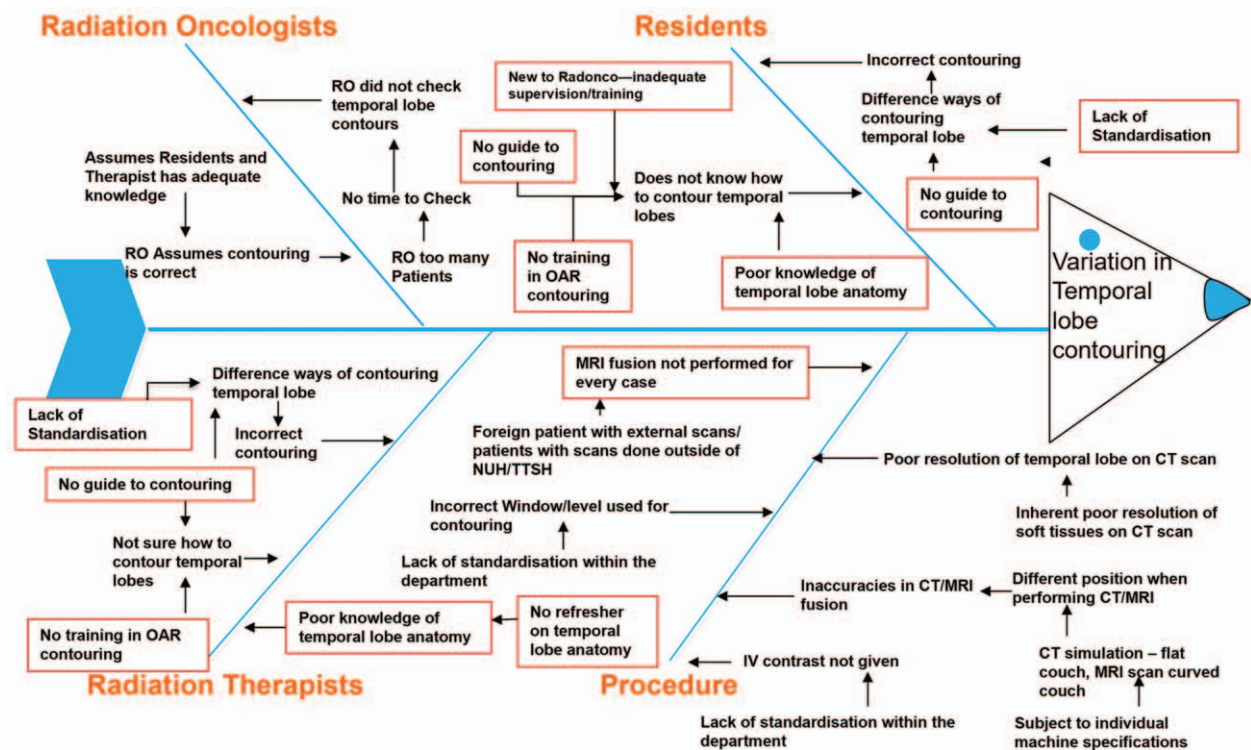
Figure 3 shows the flow chart of the temporal lobe contouring process. This allows us to identify the potential areas in the work flow that we could focus on. After consultation with the radiation oncologist, the patient is given an appointment for CT simulation. After the treatment planning CT scan is obtained with the patient in the treatment position, fusion is done to superimpose the MRI images onto the dataset obtained during planning CT to be used for treatment planning. In general, the radiation oncologists will contour the gross tumor volume and clinical target volumes. OARs, including the temporal lobe may be contoured by the radiation oncologist, resident, or radiation therapist.

We brainstormed the possible causes of variation in temporal lobe contouring and organized these causes into a cause and effect diagram shown in Figure 4.

After brainstorming, we categorized the possible causes in the variation in temporal lobe contouring and organized them into a cause and effect diagram. The broad categories include the



**Figure 3.** Flow chart of the temporal lobe contouring process. This flow chart depicts the patient flow from initial consultation with the radiation oncologist to treatment delivery. Knowing the work flow help to identify which stakeholders to target and potential areas for improvement. CI = confidence interval, MRI = magnetic resonance imaging, RO = radiation oncologist.



**Figure 4.** Cause and effect diagram. The cause and effect diagram shows that the causes of variation in temporal lobe contouring are divided into 4 categories; Radiation oncologist, Residents, Radiation therapist, Procedure. The causes within the 4 categories were further identified down to the possible root causes. These causes will then be applied to the Pareto Chart. CI = confidence interval, MRI = magnetic resonance imaging, NUH = National University Hospital, OAR = organ at risk, TTSH = Tan Tock Seng Hospital.

following: Radiation Oncologist, Residents, Radiation Therapist, and Procedure.

From the cause and effect diagram, the following root causes were identified:

1. Residents: No guide to contouring, lack of standardization of ways to contour temporal lobe, poor knowledge of temporal lobe anatomy.
2. Radiation therapists: Lack of standardization, no guide to contouring, no training in OAR contouring, poor knowledge of temporal lobe anatomy, no refresher on temporal lobe anatomy.
3. Procedure: MRI fusion not performed for every case.

**3.2. Pareto chart**

The Pareto principle states that 80% of the problem comes from 20% of the causes. Therefore using the Pareto chart, we established that 4 top causes were no standardization of volume, no training in voluming of OAR, lack of knowledge of temporal lobe anatomy and no contouring atlas to guide contouring (Fig. 5.)

**4. Intervention phase**

**4.1. Implementation and impact phases**

Improvement strategy—We focused on the top 4 causes and devised improvement interventions.

There will be a 2 sets of 2 interventions each making it a total of 4 interventions.

**4.1.1. First set of intervention.**

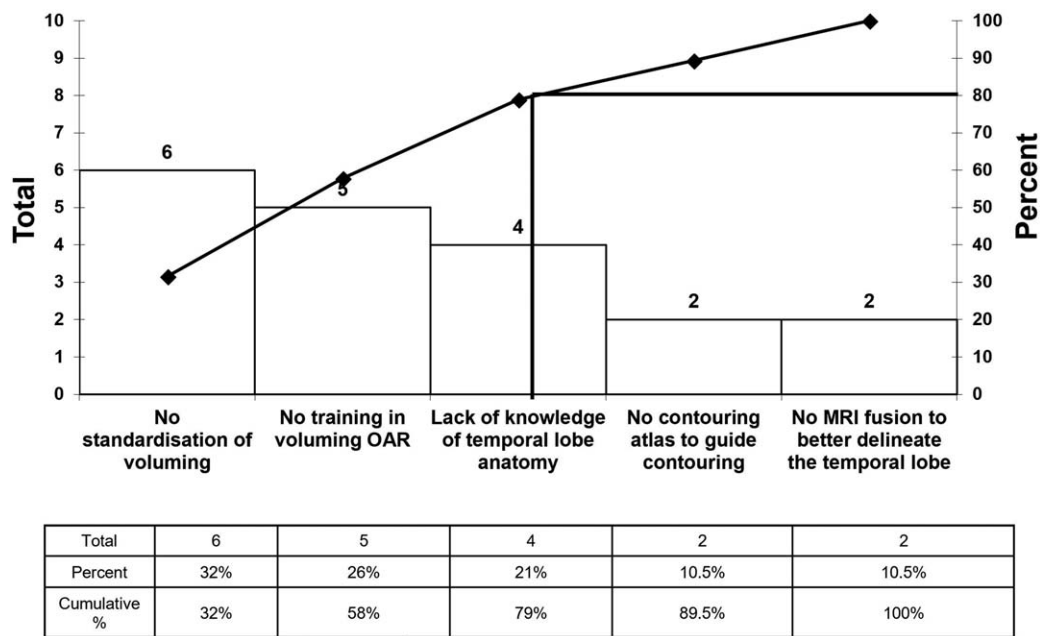
1. To improve the knowledge of temporal lobe anatomy, we will implement 6 monthly refresher tutorials to residents and radiation therapist.
2. To provide and improve training in OAR contouring, we will mandate that the radiation oncologist specializing in NPC treatment guide and supervise new therapists and residents in OAR contouring.

**4.1.2. Second set of intervention.**

1. To tackle the problem of no atlas to guide temporal lobe contouring, we will provide a CT base atlas/template for temporal lobe contouring.
2. To tackle the problem of standardization of temporal lobe voluming, we will protocolize and standardize temporal lobe anatomy and contouring. An atlas will be developed by our team, using anatomy and radiology text as reference (Fig. 6).

In view of our timeline of 6 months (June to December), we implemented the first set in the end of July 2014 and the second set in the middle of September 2014.

Two head and neck radiation oncologists FH and TC recontoured the temporal lobes of all NPC patients during the 6 months of the study. The temporal lobe contours by FH and TC were regarded as the “gold standard.” We compared the variation of the temporal lobe contour that the patient was planned and treated on with the “gold standard” contours by FH and TC. We then determined the percentage variation in temporal lobe contouring between what was contoured with the “gold standard” temporal lobe contours. Data points were



**Figure 5.** The Pareto Chart. The left vertical axis of the Pareto chart shows the total counts. Each vertical bar represents the contribution to the total from a given root cause. The bar at the left has the highest contribution to counts. The right vertical axis has percent demarcations. A cumulative line is used to add the percentages from each bar, starting at the left bar. We can see which bars contribute the most problems, and with the cumulative line, determine how much of the total problem will be fixed by addressing the highest few. MRI = magnetic resonance imaging, OAR = organs at risk.

collected every 2 weekly and plotted on a run chart to observe the percentage variation of temporal lobe contouring with time, and the effect of each set of intervention.

**4.2. Statistical analysis**

Paired *T* test would be used to compare the mean percentage variation in temporal lobe volume before and after implementation of the second set of interventions. For analyses, a *P* value of <.05 was considered statistically significant. All analyses were done using STATA 14.

**5. Results**

The project was initiated in June 2014 through December 2014. A total of 37 patients with NPC were treated during this period. An audit of the mean percentage variation in temporal lobe contouring was performed 6 months before initiation of the project from January 2014 to May 2014. The MPV in temporal lobe contouring during this period was found to be 39.9%. The CPIP workshop was held from June 3, 2014 to June 6, 2014. As seen in the run chart, there was a decrease in MPV in temporal contouring from 41.5% to 33% without any intervention (Fig. 7). The MPV increased to 43.5% in week 2 of July. This was when the first intervention was implemented. As mentioned above, refresher tutorials to residents and radiation therapists were implemented and radiation oncologists specializing in head and neck cancers supervised the contouring of the head and neck OARs, including the temporal lobes. This intervention decreased the MPV sharply down to 20%. However, the effect was not sustained and the MPV gradually rose again to peak again at week 2 of September. During week 2 of September, the team planned to implement the second intervention. The second intervention as mentioned previously is to provide an atlas/

template for temporal lobe contouring developed by the study team, as well as to standardize and protocolized the temporal lobe boundaries and contouring. At the time of implementation of the second intervention, the MPV was 39%. After the implementation of the second intervention, we had encouraging results. The MPV fell to its lowest level at 7.5% at week 2 of October. However, this was not sustained, but gradually rose again to 24% in week 4 of October. A RCA was conducted at this time, which resulted in the MPV decreasing in the subsequent weeks (week 2 of November and week 4 of November). From the run chart (Fig. 7), we can see that from the commencement of the project to week 2 of September, the average MPV was 39%. After the implementation of the second intervention, the average MPV dropped sharply to 7.5%. This was statistically significant, with a *P* value of .0004 using the paired *T* test. The pooled MPV after the implementation of the second intervention from mid September to end of November 2014 was 17.3%.

**6. Discussion**

We present the results of our quality improvement study to reduce the variation of temporal lobe contouring. In our study, we managed to reduce the MPV in temporal lobe contouring by more than 50%, from 39.9% to 17.3% in 6 months. This was achieved by the implementation of 2 sets of 2 interventions. First set of interventions included refresher tutorials to residents and radiation therapist and radiation oncologist specializing in NPC treatment, guiding and supervising new therapists and residents in OAR contouring. Second set of interventions included providing a CT-based atlas/template for temporal lobe contouring followed by protocolization and standardization of temporal lobe anatomy and contouring.

From the run chart, we can see that although the first set of interventions was implemented in the fourth week of July, there

**Guide to Temporal Lobe Contouring for radiotherapy planning**

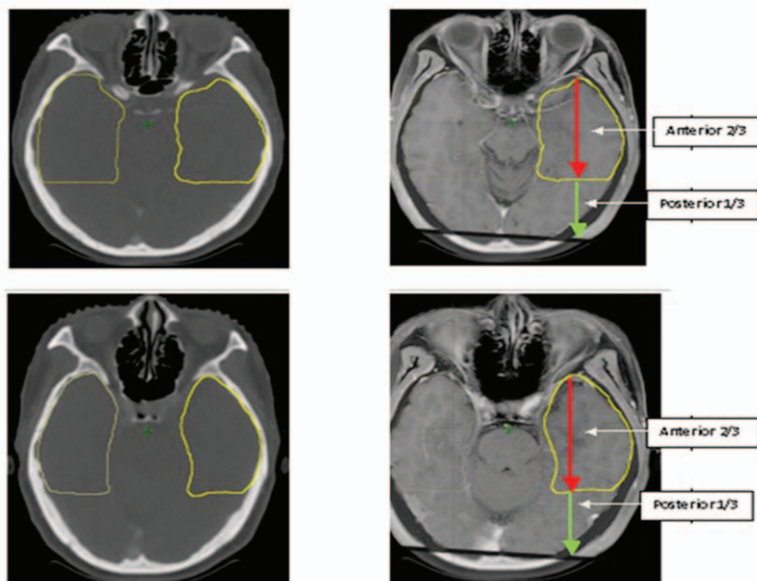
Appearance of temporal lobe

Crescent-shaped portion of cerebrum lying within middle cranial fossa  
 Comprise of: Grey + White matter

Boundaries

|           |  |
|-----------|--|
| Inferior  | Base of skull (squamous portion of temporal bone + greater sphenoid wing)<br>Tentorium cerebelli (attached to petrous temporal bone) |
| Lateral   | CSF space medial to temporal bone  |
| Medial    | Inferiorly: CSF space surrounding brainstem + tentorium cerebelli<br>Superiorly: midbrain + lateral ventricles                       |
| Superior  | Lateral (Sylvian) Fissure- easiest traced from lateral aspect  |
| Anterior  | CSF space posterior to Greater wing of sphenoid  |
| Posterior | Imaginary line dividing cranium into anterior 2/3 and post 1/3   |

Window: Brain Window



**Figure 6.** Protocol and guide to standardize temporal lobe contouring. This figure shows the protocol for landmarks to be used for temporal lobe contouring. The magnetic resonance imaging (MRI) images provides an atlas for contouring the temporal lobe on axial slices for both the computed tomography (CT) and MRI images. This is used to standardize the contouring of the temporal lobes. CSF = cerebral spinal fluid.

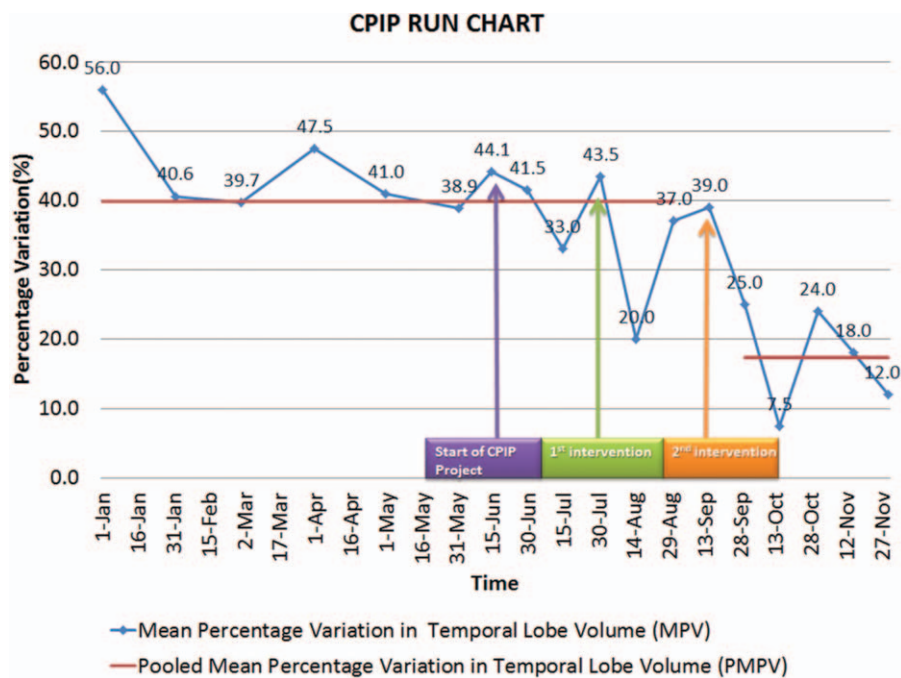
was a dip in the MPV from 41.5% to 33% in June. This was likely due to increased awareness that a Quality Improvement Project to improve temporal lobe contouring was being planned in the department. Because of increased awareness, the staff may have been more cognizant in contouring the temporal lobe more accurately, with the resultant decrease in MPV. However, this decrease was not sustained and the MPV quickly rose again to 43.5% in the next 2 weeks.

After we implemented the first set of interventions, the MPV dropped sharply to 20%. This drop was again not sustained, as the MPV rose gradually again to 39%. There could have been several reasons for this. Firstly, the refresher tutorials which were planned to occur every 6 months were not adequate to reinforce temporal lobe anatomy to the residents and radiation therapists, suggesting that tutorials at more frequent intervals, such as monthly may be

required. Secondly the radiation oncologist might not have had time to supervise the temporal lobe contouring for each and every patient. Thirdly, the interpretation of what is correct temporal lobe anatomy might differ from one staff to another.

We implemented the second set of interventions in week 2 of September, and had encouraging results with a sharp drop in MPV to 7.5%. In week 4 of October, we noticed yet another spike in the MPV. After an RCA, we discovered that some of the radiation therapists were away at the time of implementation of second set of interventions, and were not aware of that there was an atlas and template available to guide temporal lobe contouring. After this RCA, we noticed that there was a sustained decrease in the MPV in November.

Our team felt that this study was important and timely. Nelms et al<sup>[13]</sup> showed that the variation in OAR contouring can affect



**Figure 7.** CPIP Run Chart. From the chart, we can see after the implementation of the first set of intervention, the MPV fell to 20%. This rose to 39% in the first half of September 2014. After the second set of the interventions at this point, the MPV fell to 7.5%. From the commencement of the project to week 2 September, the average MPV was 39% (red line). After the implementation of the second intervention, the average MPV dropped sharply to 7.5%. This was statistically significant, with a *P* value of .0004 using the paired *T* test. The pooled MPV after the implementation of the second intervention from mid September to end November 2014 was 17.3%. CPIP = Clinical Practice Improvement Program.

the final treatment plan and that the variations in contouring of OAR ranged from  $-289\%$  to  $56\%$  for mean OAR dose and  $-22\%$  to  $35\%$  for maximum OAR dose. In the era of IMRT, accuracy and reproducibility of OAR contouring, in addition to tumor target volumes becomes increasingly important.

The impact of accurate temporal lobe contouring is considerable. The clinical outcome of temporal lobe necrosis can be debilitating. Patients with radiation-induced temporal lobe necrosis were found to have significant impairment on tests of verbal and visual memory, language, motor ability, planning, cognitive ability, and abstract thinking compared against patients who received radiation but did not develop temporal lobe necrosis. The overall cognitive impairment greatly affects the employability of these cancer survivors.<sup>[14]</sup> Even with a conservative estimate of incidence of temporal lobe injury after NPC irradiation at 5%, this represents 6 patients out of the 120 patients we treat every year at our institution. Assuming that we are able to reduce the risk of temporal lobe necrosis by one third with improved and accurate contouring of the temporal lobes, the financial impact of this project would be represented by:

Cost of 2 patients/year having temporal lobe necrosis with subsequent morbidity and loss of income = 65 (average age of retirement) – 50 (median age of NPC development) × income per year × 2 per year.

Furthermore, accurate temporal lobe delineation becomes even more critical where the tumor volume comes in close proximity to the temporal lobes and accurate treatment and delivery of radiotherapy to the tumor is of clinical importance.

Although we were successful in reducing the variation in temporal lobe contouring after the implementation of our project, we recognized the need for long-term sustainability. The strategies for long-term sustainability will include periodic

meeting (3 monthly) with radiation therapists and residents to identify areas for improvement and to clarify any difficulties encountered; secondly, to increase awareness of the proper temporal contouring by providing atlases/guidelines at all planning stations; thirdly, to conduct 3 to 6 monthly refresher for residents and radiation therapists; and lastly, to conduct random audit of 1 patient every month with thorough study (RCA) of spikes.

The strengths of this study are that this is the first study to our knowledge to report the use of a systematic approach to improve the accuracy of temporal lobe delineation. Data were prospectively collected and we followed the CPIP methodology which applies evidenced-based medicine within a clinical improvement project. The limitations are that the patient numbers were relatively small in this study and we require long-term follow-up to determine the impact of our study on NPC patients treated with head and neck radiotherapy.

## 7. Conclusion

We managed to improve the accuracy and decreased the variation in temporal lobe contouring by 50% over a 6-month period. We have plans to further implement this in other OAR with the same methodology to further improve quality assurance in radiotherapy contouring which will ultimately translate into clinical benefit for our patients.

## Author contributions

JT designed the study protocol. JT, FH, DC, YYS, CWT, SB, TC, and IT implemented the protocol and oversaw the collection of the data. JT and FH performed plan data analysis. JT and FH



wrote the manuscript. JT, FH, DC, YYS, CWT, SB, TC, and IT reviewed and approved the final manuscript.

**Conceptualization:** Francis Ho, Jeremy Tey, Yu Yang Soon, Timothy Cheo, Ivan Tham.

**Data curation:** Francis Ho, Jeremy Tey.

**Formal analysis:** Francis Ho, Jeremy Tey.

**Methodology:** Jeremy Tey, David Chia, Yu Yang Soon, Chek Wee Tan, Timothy Cheo, Ivan Tham.

**Project administration:** Jeremy Tey.

**Resources:** Jeremy Tey.

**Supervision:** Francis Ho, Jeremy Tey, Chek Wee Tan, Sarahatul Bahiah, Timothy Cheo, Ivan Tham.

**Writing – original draft:** Francis Ho, Jeremy Tey, David Chia, Yu Yang Soon, Chek Wee Tan, Sarahatul Bahiah, Timothy Cheo, Ivan Tham.

**Writing – review and editing:** Francis Ho, Jeremy Tey, David Chia, Yu Yang Soon, Chek Wee Tan, Sarahatul Bahiah, Timothy Cheo, Ivan Tham.

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