Expert opinions on Robotic CyberKnife Technology

Manaswini Pattanayak[1], Edi Laxmi [2]

[1]Asst. Professor, Einstein Academy of Technology & Management, Bhubaneswar
[2]Professor, Einstein Academy of Technology & Management, Bhubaneswar

ABSTRACT
Robotic Cyber knife (CK) is an advanced robotic Stereotactic Radiosurgery technology that is used in Radiation oncology to treat brain and body tumours in cancer patients. The aim of this study was to find out and compare how Cyber knife Image guided technology is being used in two active clinical Cyber knife centres in USA and Australia to provide treatment to patients with brain and other cancers. The expert opinions of a medical physicist and a Medical Radiation therapist with clinical experience of using Cyber knife were captured using an E-questionnaire. This study assessed clinical, technical, organizational and Educational strategies and resources employed to provide Cyber Knife treatment in two clinically active CK centres. This study was done in 2020.

KEYWORDS: *Brain tumours, CyberKnife,Image guided Radiotherapy, Real-time tracking, Stereotactic body Radiotherapy, Stereotactic Radio surgery.*

I. INTRODUCTION

Robotic Photon based CyberKnife Image guided Radiotherapy is currently being used in certain institutes globally to provide Stereotactic radiation treatment for intra and extra cranial tumours. The CyberKnife System is developed by Accuray Incorporated, Sunnyvale, California, USA[1]. The CyberKnife system delivers both radiosurgery (SRS) and frameless stereotactic body Radiotherapy (SBRT). The definition of SBRT is provided by Stereotactic Radiotherapy working group upon the request from German Society of Radiation Oncology and this definition is agreed by other working groups in different countries. According to thisdefinition SBRT is a form of external Beam Radiotherapy that delivers highly conformal high radiation doses in few fraction with image guidance. SBRT also involves active or passive intrafraction motion management and follow up [2].

The CyberKnife System consists of six main components namely i) a 6 MV linear accelerator mounted on ii) a robotic arm and iii) a tumour tracking system (In-room stereoscopic KV x-ray system with in-floor detectors, iv) Respiratory motion management system (Synchrony), v) treatment couch with 5 degree of freedom and vi) an algorithm that connects the tumour motion with chest wall motion in order to predict tumour motion at all times during the treatment[1]. Synchrony system monitors patients' breathing in real time and consists of Infrared Light emitting diodes placed on patient's thorax along with wall mounted infrared detector or camera. It ensures that linear accelerator is synchronized with target that moves due to respiration.

CyberKnife has five tracking options namely 6D Skull, X Sight spine, X Sight lung with Synchrony, Fiducial with Synchrony, and Fiducial [3]. XSight tracking system that is good for spine tumours but is not good for abdominal tumours which are positioned distal to spine [4]. CyberKnife system provides AI driven real time tumour tracking of implanted fiducial markers and respiratory motion management to ensure treatment accuracy by constantly identifying and correcting for tumour and radiation beam mismatches throughout the entire treatment. The use of CyberKnife is increasing globally and it is first SBRT and SRS technology that provides real time tumour tracking. Above all CK treatment is associated with sharp dose fall. These features of CK technology ensures accuracy in treatment delivery and therefore is likely to result in use of reduced treatment margins resulting in better sparing of Organs at risk. This in turn ensures dose escalation resulting in potentially better tumour control and reduced treatment induced side effects. The purpose of the study was to gather opinions of CK experts to find out how Robotic photon based Cyber knife Image guided technology is being used to provide treatment to patients with brain and other cancers. The study wants to identify variations in dose

prescription and margin and tumour tracking methods. The present study discusses how Cyber Knife technology is used in two Institutions based in Australia and USA, what clinical, technical and organization resources are used to impart CK treatment, what challenges were faced during its implementation and what improvements are sought in the CK technology by the experts. The study also recorded what education and training pathways are used to impart CK knowledge. The present study gives a synopsis of similarities and differences in employing CK technology for management of various cancers.

II. MATERIALS AND METHODS

A. Study Overview An expert opinion E-survey was designed to gather opinions and views of Radiation Oncology professionals who have expertise in CyberKnife Treatment Planning, delivery and dosimetry.LinkedIn platform (Social Media) was used to contact experts of CyberKnife technology. Two experts based in CyberKnife centres in Australia and USA agreed to fill in the survey and the E-survey was sent to them via LinkedIn. The study was conducted in 2020.

B. Selection of case studies and E-Survey The questionnaire was designed in MS word and consisted of 33 questions, most of which were close ended questions. Survey questions were structured in five sections namely i) Demographic, ii) CK institutional background Information, iii) CK information, iv) Treatment planning and delivery, v) Knowledge and Experience. Appendix A shows sample E-survey.

C. Ethical Considerations This study was deemed IRB exempt as it was a quality enhancement and evaluation study. Responses were anonymous so no ethical approval was required. No patients were approached. No medical or personal data of participants collected. By answering the questionnaires, the professionals agreed to give their informed consent.

D. Statistical Analysis

Data was recorded and analysed in Microsoft Excel. Descriptive analysis was used to examine the results of the study.

III. RESULTS

A. *Respondent Characteristics*: 100% of the respondents were male. 50% of respondents belonged to 30-40 years of age range and the other 50% belong to 50-70 years of age range. both respondents were married (100%). One respondent was Medical Radiation Therapist from Australia and other was Medical Physicist from USA. Medical Physicist from US has 10 years of Clinical Experience of CK (50%) whereas Medical Radiation Therapist from Australia had 5 years of clinical experience. Results are show in Figures 1-3

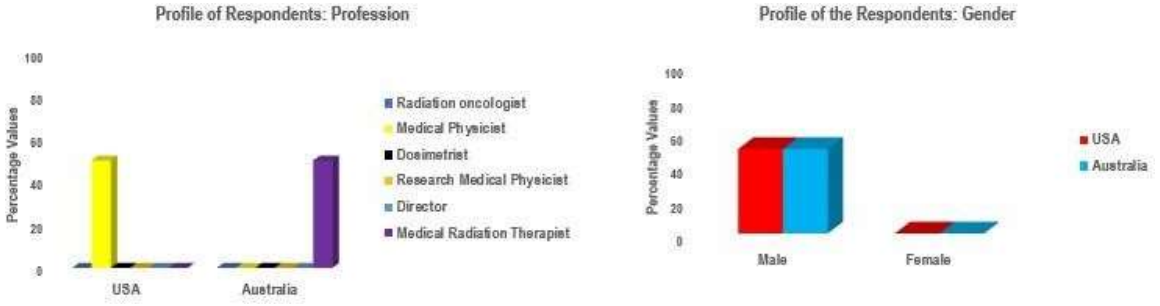


Fig.1 Socio Demographic Profile of Respondents: Gender

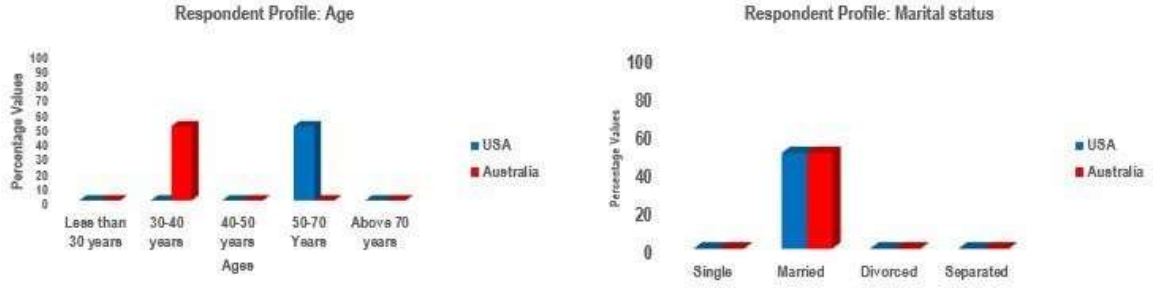


Fig. 2 Socio Demographic Profile of Respondents: Age and Marital status

Fig. 3 Clinical Experience of CK

B. CK institutional Background and Resources

1. Do you have CK in your hospital or Institution?

The respondent from USA (50%) said there was no CK in his hospital whereas Respondent from Australia had CK (50%).

2. **Location of the Institute and Type of Practice**

One respondent 950%) was from Nevada, USA and the other from Perth Australia (50%). Results are shown in Fig 4-5.

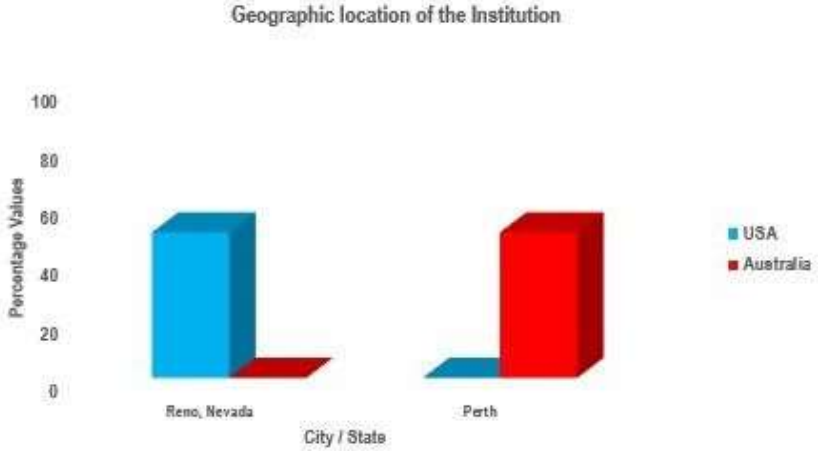


Fig. 4: Location of CyberKnife Centres

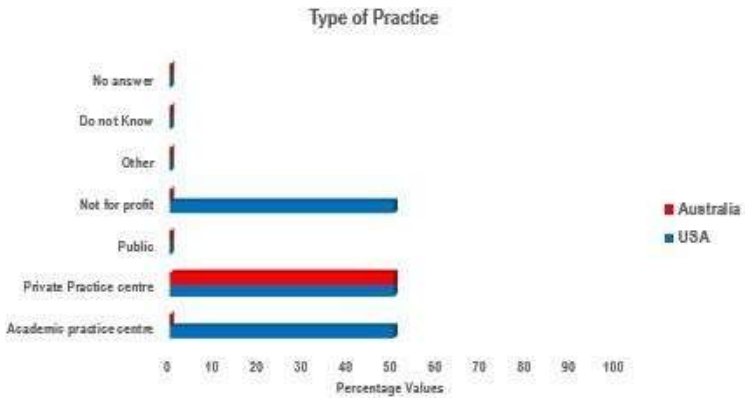


Fig. 5 Type of practice

3. **Professionals involved in CK delivery**

Respondent from USA said that two medical physicists (13.3%), one radiographer (6.7%), four Radiation therapy Technologist (26.7%), three radiation oncologist (20%) and 5 neurosurgeons (33.3%).
whereas respondent from the Australia only mentioned that medical physicists, radiographers, radiation technologists, dosimetrist andradiation oncologists all are involved in CK treatment planning and delivery but did not specify their number. Results from US case study are shown in Fig. 6.

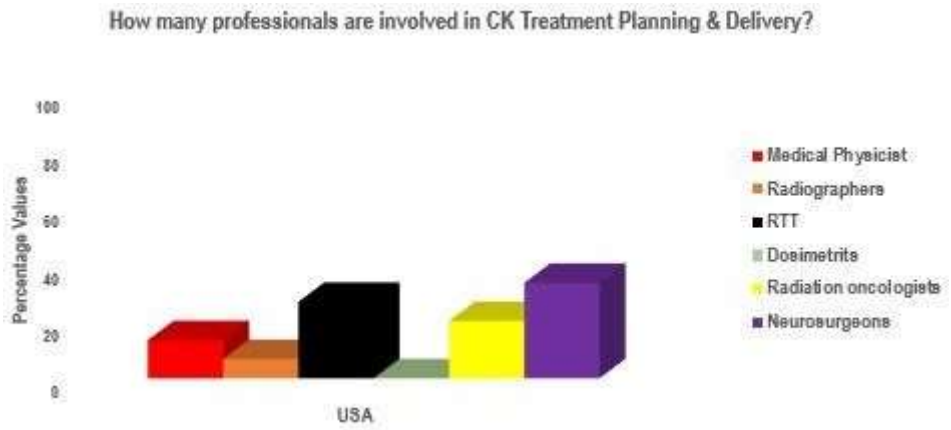


Fig. 6 CyberKnife Team

4. **Technical, Clinical & Organizational Challenges**

The respondent from Australia said they experienced financial difficulties while respondent from US said they experienced no challenges in implementing CK. Results are shown in Fig.7

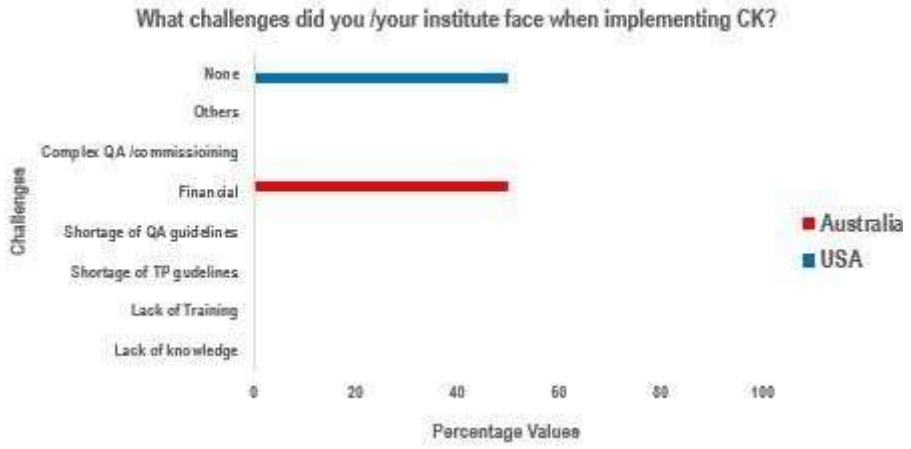


Fig. 7 Challenges

C. Information about CK Technology

1. Intent

The respondent from Australia said CK is used for both Curative and palliative purposes whereas the Medical physicist from US said CK is used for curative purposes. Fig.8 shows the results.

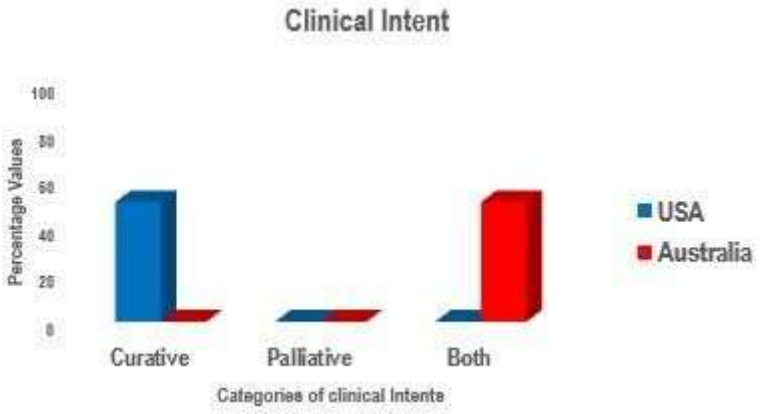


Fig. 8 Clinical Treatment Intent

2. Type of tumours

Both respondents from Australia and US said they use CK to treat both Intracranial and body tumours as well as for primary and metastatic tumours. Results are shown in Fig. 9-10

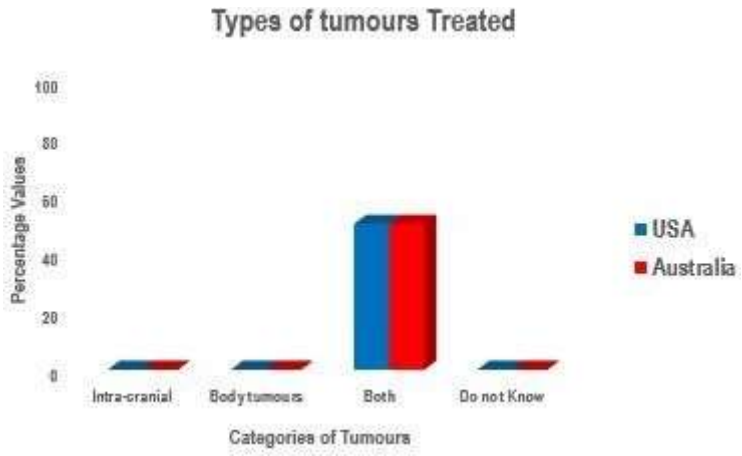


Fig. 9 Tumour Types

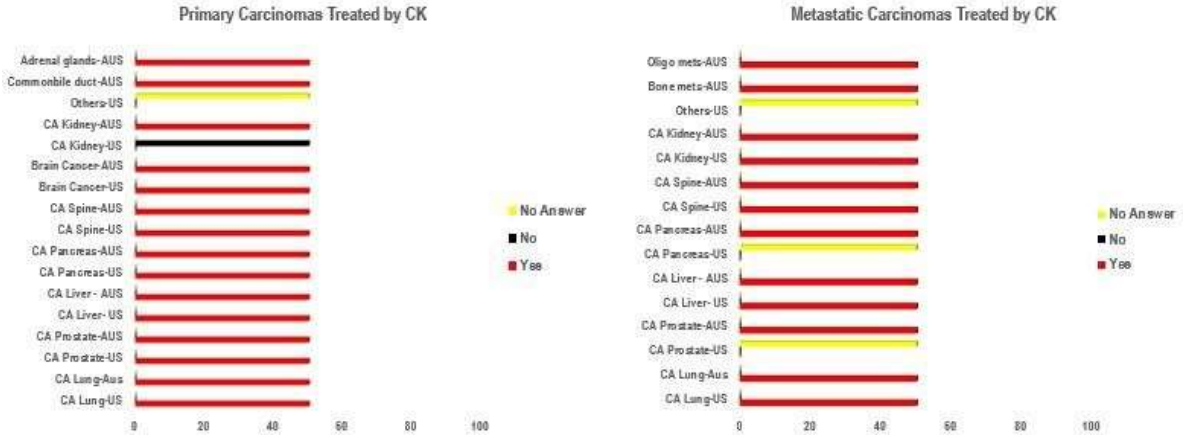


Fig. 10 Primary and Metastatic tumours

3. Stage

Respondent from US said CK is only used for early stage cancers whereas respondents from Australia said CK is used for both Early and advanced stage disease in their hospital. Results are shown in Fig.11

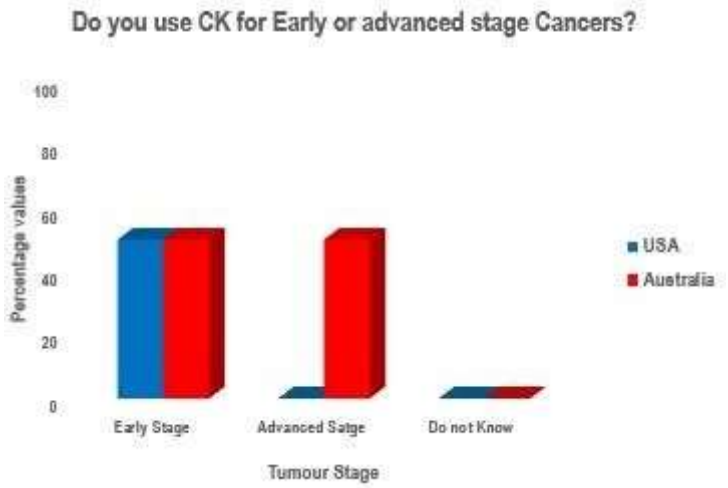


Fig.11 Tumour Stage

4. Reasons for CK adoption in the department/organization

Results are shown in Table I.

Table I
CK Adoption

Reasons for CK Adoption	
USA	**Australia**
	Dose Escalation
Precise treatment delivery	Precise treatment delivery
Better local control rates	Better local control rates
	Treatment time reduction
Retreatment	Retreatment
	Clinical Research
Gain Competitive edge	Gain Competitive edge

D. Treatment Planning and Delivery

1. CK Image Guidance System

In response to the question what CK image guidance system consists of both respondents mentioned tracking. Results are shown in Table II.

Table II : CK components

Components of CK IGRT	
USA	**Australia**
Tracking Using Orthogonal KV system	Skull Tracking
	Spine Tracking
	Synchrony with fiducial
	1 view lung
	2 view Lung
	Fiducial Tracking

2. Other IGRT Systems

In response to the question what type of Image guidance you use to localize target & verify target before treatment delivery responders stated various IG systems in addition to CK image guidance. Results are shown in Table III

Table III Image guidance

IG used for Target Localization& Verification	
USA	**Australia**
	In room volumetric imaging
	Planar imaging
CK image Guidance System	CK Image Guidance System
Fiducial Marker (Except for brain, spine & most lungs)	Fiducial Markers
During treatment: Imaging for continuous tracking	

3. Immobilization

Various immobilization devices are used in conjunction with CK treatment. Results are shown in Table IV.

Table IV
Types of Immobilization applied during CK

Immobilization Techniques/Devices		
Cancers	**USA**	**Australia**
CA Lung		
CA Prostate		
CA Liver (HCC)		
CA Pancreas		
Spinal Cancer	Mask for C-spine	
Brain Cancer	Mask	Head Frame
Kidney Cancer		
Others		

4. Treatment dose and fractionation

Different dose regimes are used in US and Australia. Results are shown in Table V.

Table V
Dose Regimes

Most Common Dose Regimes		
Cancers	**USA**	**Australia**
Primary Localized PC	36.25Gy in 5#	35-36Gy in 5#
Metastatic PC	Boost	35-36Gy in 5#
Primary Lung Tumour (ES)	60Gy in 3 or 5#	54Gy in 3#
Primary Lung Tumour (AS)		54Gy in 3#
Metastatic Lung cancer	60Gy in 3 or 5#	54Gy in 3#
Recurrent lung cancer	50-60Gy in 5#	54Gy in 3#
Primary Unresectable small HCC	No answer	45Gy in 3#
Primary large unresectable HCC	No answer	45Gy in 3#
Liver Metastases	No answer	54Gy in 3#
Recurrent Unresectable HCC	No answer	54Gy in 3#
Primary Spinal lesions	No answer	27Gy in 3#
Metastatic spinal lesions	No answer	27Gy in 3#
Primary Pancreatic lesion	No answer	40Gy in 5#
Metastatic Pancreatic lesion	No answer	40Gy in 5#

5. Margins

In response to the question how much margin you apply to GTV to get CTV, respondent from US stated zero CTV margin for listed cancers whereas respondent from Australia stated 2mm margin for both advanced and early stage primary lung carcinomas. Results for both CTV and PTV are shown in Fig. 12-13 and Table VI.

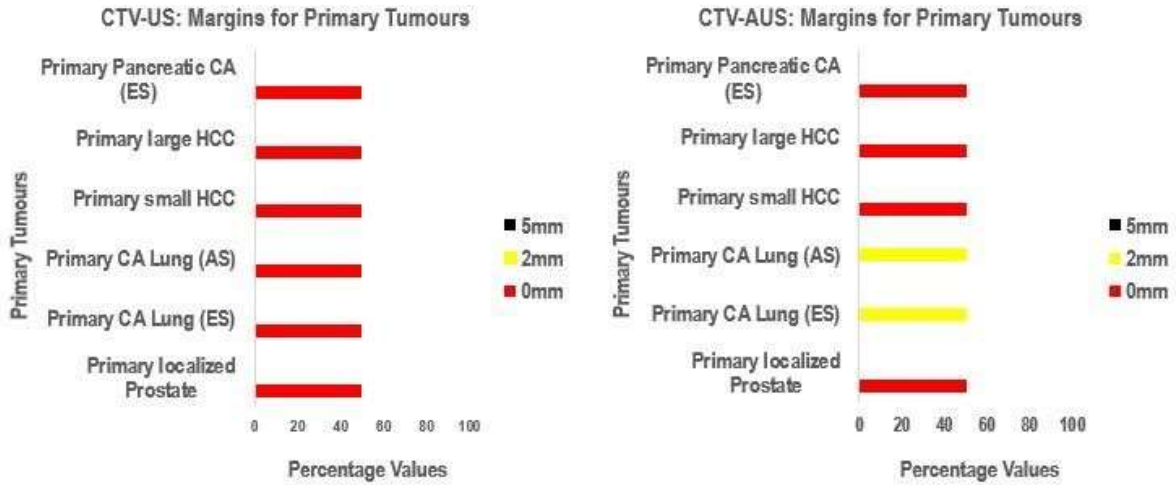


Fig. 12 CTV=GTV+margin

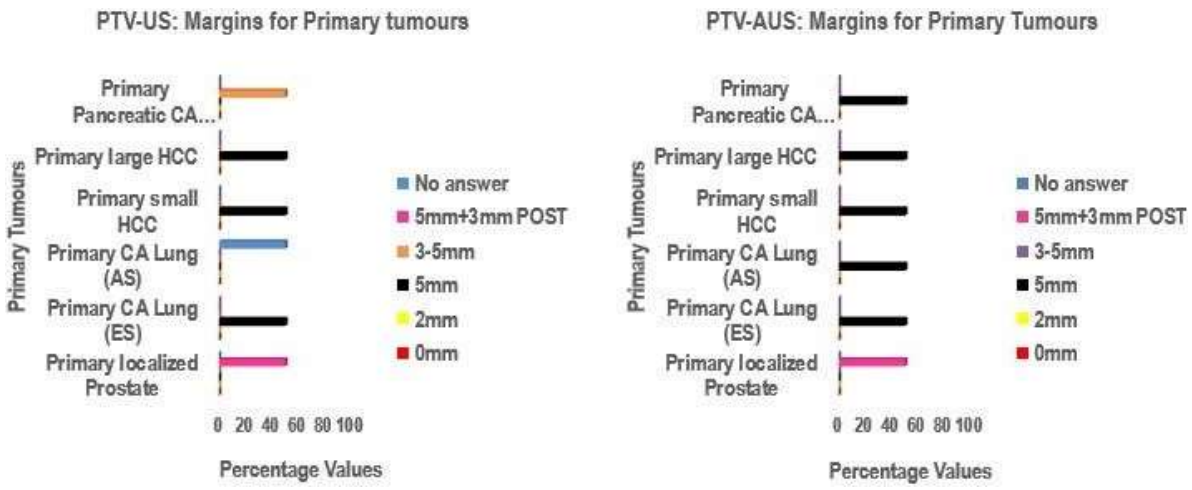


Fig. 13 PTV = CTV + margin

Table VI
Margins for Metastatic Disease

Cancers	USA CTV=GTV + Margin	USA PTV=CTV + Margin	Australia CTV=GTV+ Margin	Australia PTV=CTV+ Margin
Spinal Metastases	0	1mm	0	0
Liver Metastases	0	5mm	0	5mm
Localized Pancreatic cancer (ES)	0	3-5mm	0	5mm
Metastatic PC	0	Boost	0	5mm+3mm post

6. Beam Energy

Both respondents said they use 6MV for various tumours. Results are shown in Fig. 14

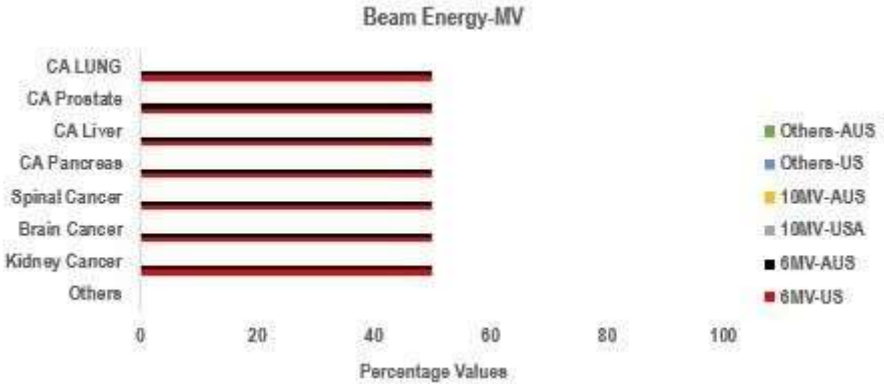


Fig. 14 CK System Beam Energy

7. TPS and Radiation treatment planning

The medical Physicist in US said CyberKnife Multiplan Treatment planning system (50%) is used whereas respondent from Australia said Accuray Precision radiotherapyTPS (50%) is used for CK radiation treatment planning. In Australia Radiation Technologist whereas in US Medical Physicist perform CK radiation treatment planning. Results are shown in Fig. 15-16.

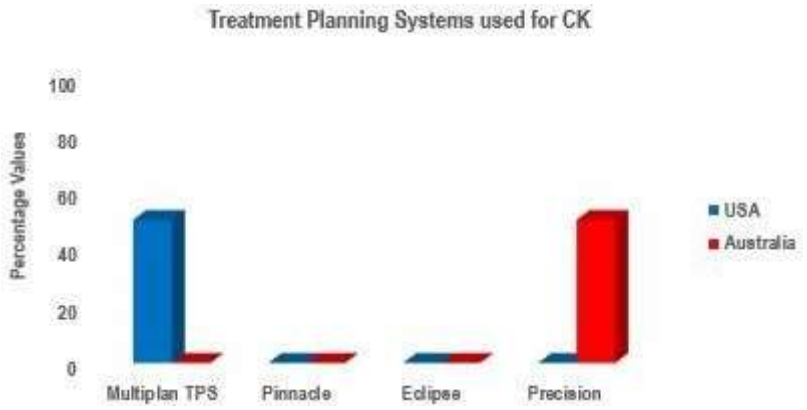


Fig. 15 CK TPS

Fig.16 Professions responsible for Treatment planning

8. Motion management

In response to the question which technique is employed to manage breathing induced motion,bothrespondents(100%) said they use fiducial markers and Synchrony™ Respiratory tracking system (real time tracking). Results are shown in Table. VII-VIII

Table VII
Motion Management Techniques-USA

Cancers	**USA** Fiducial Marker	USA **Synchrony™**	**USA** Breath hold	**USA** Other
Ca lung	Y	Y	N	-
CA prostate	Y	N	N	-
CA Pancreas	Y	Y	N	-
CA liver	Y	Y	N	-
CA Kidney	Y	Y	N	-

Note: Y= Yes, N=No, CA=carcinoma

Table VIII
Motion Management Techniques-Australia

Cancers	**AUS** Fiducial Marker	AUS **Synchrony™**	**AUS** Breath hold	**AUS** Real time tracking
Ca lung	Y	Y		-
CA PC	Y	N		Y
CA Pancreas	Y	Y		-
CA liver	Y	Y		-
CA Kidney	Y	Y		-

Note: Y= Yes, N=No, CA=carcinoma

9. **Common toxicities:**respondent from Australia said fatigue and tiredness was most common acute toxicity experienced by patients suffering from prostate, liver, pancreas and kidney cancers. Respondent from USA did not answer the question.

10. **CK vs. IMRT vs. VMAT vs. Proton Therapy:**in the view of expert from US, CK treatment provides better tumour control, Disease free survival (DFS), Overall survival (OS) and reduced CK treatment induced morbidity compared to IMRT,VMAT and proton Therapy. The CK Expert from Australia said it is a complex question and cannot be answered.

E. Knowledge and Experience

Results are shown in Fig.17-19

Fig. 17 Pathways for achieving CK Education & Training

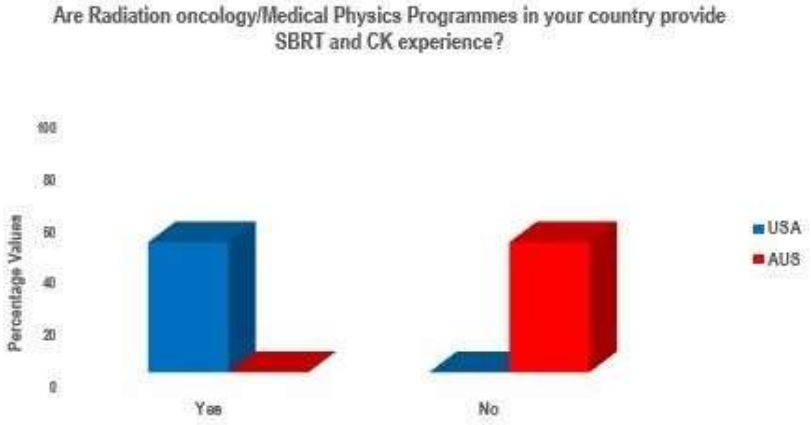


Fig. 18 CK Experience

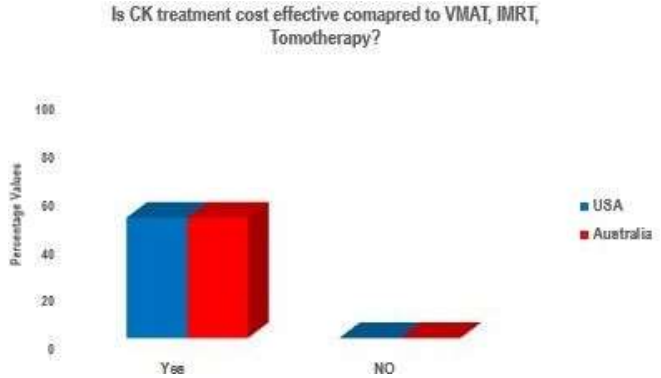


Fig. 19 CK Cost Effectiveness

IV. DISCUSSION

Discussion

The present study provides a description of current practices of Robotic CK as well as clinical, technical and organizational resources used in imparting CK treatment for treating both intracranial and extracranial tumours in Australia and USA.

The present study is unique as it compares the CK practices, resources and strategies via Expert opinions in two institutions (case studies) based in widely different geographical regions. The present study collated the data on Profession, Gender, age, Marital status and Clinical experience of CK experts under the category of demographic Information.

Both CK experts had significant clinical experience of using CK (Australian Expert: 5 years, USA Expert: 10 years). The respondent from Australia was Medical Radiation Therapist based in a private hospital in Perth while respondent from the US was a Medical Physicist currently working in a private not for profit academic centre in Nevada. He previously worked in another centre that had CK facility.

Consensus differed between the two experts with regards to Challenges faced during CK implementation in the department, number and types of professionals required for CK treatment planning and delivery, Intent of CK treatment, stage of the disease, RT dose and fractionation. In the present study, the respondent from Australia said they experienced financial difficulties while respondent from US said they experienced no challenges in implementing CK. A paper by Dieterich and Pawlicki [5] highlights the complexity of QA program for CyberKnife in clinical practice and recommend that frequency of QA checks should be based on clinical studies rather than on historical benchmarks established for massively different technologies. The study also recommends formation of phantoms appropriate for distinctive QA needs of CyberKnife system.

In terms of similarities of CK practices, CK technology is used to treat both intracranial and extra-cranial tumours. CK is also used to treat both primary and metastatic disease in both case studies. However there was some differences. Expert from USA said CK is used to treat primary lung, prostate, liver, pancreas, spinal and brain tumour but not used to treat primary kidney tumours in his centre. He also said metastatic tumours of lung, liver, spine, brain and kidney are treated by CK. Expert from Australia said that CK is used in his centre to treat both primary and metastatic tumours of Lung, prostate, liver, pancreas, spine, brain, kidney, CBD (Common bile duct), adrenal tumours. In addition to it in Australia CK is used to treat bone metastasis and oligo metastasis. Literature review also shows that CK is treated for various primary and metastatic tumours [6–8].

In the present study Different doses were reported for lung cancers by both experts (60 Gy in 3-5# in USA vs. 54Gy in 3# Australia). Most common dose was spinal cord tumours was 27Gy in 3 fractions, for liver tumours 45 Gy - 54 Gy in 3 fractions, for prostate cancer was 35-36Gy in 5 fractions and for pancreatic tumours 40Gy in 5 fractions. In the present study fatigue and tiredness were most common acute toxicity experienced by patients suffering from prostate, liver, pancreas and kidney cancers.

In the present study no margin was added to GTV to obtain CTV for **localized prostate disease** and a margin of 3mm posteriorly and 5mm anteriorly and laterally was added to obtain PTV. This is in line with the literature. Both respondents from US and Australia reported using 3-5 mm margin around GTV to obtain PTV for **localized pancreatic cancer**. This is similar with the margins used in Song et al. [9] study who expanded GTV by 3mm to get PTV. **. In the present case studies a margin of 2mm was added to achieve PTV for spinal metastases in USA case study and a margin of zero in Australian case study. A margin of 5mm was reported in both** case studies for liver metastasis. These margins are similar to margins reported by Kato et al. [10] in liver cancer patients.

Dose Regimes, Margins and Radiation induced Toxicity:

NSCLC studies

There is 0% risk of developing radiation myelitis when treated with hypo-fractionated regimes of 8Gy in 1 fraction to 4Gy in 5 fractions [11-12]. A review of three randomized trials of palliative RT in 114 NSCLC patients showed no spinal myelopathy when treated with 10Gy in one fraction. However patients treated with 17Gy in 2 fractions had a cumulative risk of 2.2 % of developing myelopathy at 2 years. Further data has shown that Spinal cord can tolerate 10Gy to 10% of the volume as defined as 6 mm above and below the target lesion with acceptable rates of myelitis [13].

A study by Collins et al. [14] treated 20 patients with inoperable Stage 1 NSCLC with CK in Georgetown University Hospital, Washington DC, US. Dose ranged from 42-60Gy in 3 fractions and median follow up of surviving patients was 25 months with an overall survival estimate of 87%. The present study also reported doses for primary and metastatic lung cancers range from 54 – 60Gy in 3#.

Spinal tumours/metastases and Re-irradiation studies:

A number of studies have shown no radiation induced myelopathy after a Biological effective dose of 80-100Gy to spinal cord at a median follow up of 8 months [15-17]. Patients receiving BED > 102 Gy seems to show myelopathy [18]. Another study has concluded that a point maximum dose of 10Gy is safe as radiation induce myelopathy was found to take place when maximum point doses are 14.8, 13.1 and 10.6 Gy in a single fraction [19].

In the present study either no margin or a margin of 1mm was used around CTV for treatment of spinal metastases with a dose of 27Gy in 3 # (9 Gy /#). This seems to be safe dose with probably a low and acceptable cumulative risk of myelopathy, with high probability of tumour control and symptom relieve.

Yamada et al.[20] reported no myelopathy or other late toxicities in 93 patients that were treated with a median dose of 24 Gy (range 18-24Gy) with spinal cord maximum point dose restricted to 14 Gy. After a median follow up of 15 months, the actuarial 1 year control rate was 90%. This study found a direct dose - response relationship i.e. higher doses give rise to better local control rates. The spinal radiosurgery was conducted in Memorial Sloan-Kettering hospital.

A phase I/II trial conducted at the MD Anderson Cancer centre treated 63 patients with hypo-fractionated course of spinal radiosurgery with a fractionated regime of 6 Gy in 5 fractions to half the patients and 9 Gy in 3 fractions given to other half. No grade 3 or 4 neurologic toxicity or myelopathy was reported with a median follow up of 21 months and the one year actuarial progression-free rate was 84%. The study reported one case of grade 3 nausea, vomiting and diarrhea, one case of grade 3 dysphagia and trismus and one case of grade 3 non cardiac chest pain. The study recommended using wide posterior margin to diseased vertebrae to avoid recurrence in bone adjacent to the spinal cord and in epidural space [21].

Brain tumour studies:

A study by yang et al. [22] showed that CyberKnife treatment is effective in treatment of metastatic brain disease. A patient with more than 24 brain lesions was treated with CyberKnife and was given a total dose of 22Gy in 3 fractions showed complete disappearance of the tumour 3 months post treatment

A retrospective study by Acker et al. [23] showed safety and efficacy of CyberKnife treatment in elderly patients with brain metastases. The projected overall survival at 3, 6 and 12 months after treatment were 79, 55 and 23% respectively while the and local tumour progression free survival at 6, 12, 36 and 72 months post treatment were 99.2, 89.0 and 67.2, 64.6 and 64.6% respectively. The predictive factors for local progression were Older age and female sex. The study reported Karnofsky performance score remained steady in 97.9% of the patients.

Another study by Telentschak et al. [24] reported actuarial local control rates at 3, 6, and 12 months were 98%, 98%, and 78.6%, respectively in patients with critical brain metastases. 12 % of patients had grade I to III complications. The study found that median overall survival was associated with higher KPS.

Liver tumours studies: A study conducted by Kato et al. [10] 65 advanced and terminal stage HCC patients (with 95 lesions) with CyberKnife and reported better survival with doses greater than or equal to 30 Gy. Out of 52 cases of bone metastases, 69% of patients achieved pain relief. Toxicity included grade 4 Cerebral bleeding in one patient treated for brain metastases and grade 2 oesophageal ulcer in another patient post treatment who was treated for hepatic vessel lesion (Complete response was achieved with 31.2Gy to oesophagus) The Treatment Planning system (TPS) used was MultiPlan® (Accuray) and Synchrony® (Accuray) tracking system was used to track the tumour. The Planning target volume for intra-hepatic lesions and lung metastases include **GTV plus 2-5 mm margin in all directions** whereas the PTV for **spinal lesions** included **GTV plus 2 mm margin** and for brain metastases no margins were applied to GTV. Total dose ranged from 8-50Gy, delivered in 1-10 fractions and prescribed to the 80% isodose line administered to the PTV over 1-7 consecutive working days. The median prescribed dose for tumours invading hepatic vessels or bile duct was 35 (range : 28-50 Gy) in 3-10 fractions where as median prescribed dose for extrahepatic lesions was 25 Gy (6-48) in 1-6 fractions. The response rate was 48% and disease control rate was 76% for all lesions after excluding unevaluated cases. The response rate and disease control rates for tumours invading the hepatic vessels or bile duct were 50% and 80 % respectively. As far as adverse effects are concerned no patient had a grade 2 or higher toxicity. No classic Radiation induced Liver disease, considerable rises in liver enzyme and haemotologic complications were detected during treatment. **Compared with these results, the margins and doses reported in the present case studies are similar.** The most common dose was 45Gy in 3 fractions for primary liver tumours and 54Gy in 3 fractions for liver metastases in the present study which is above 30Gy. However doses for spinal metastasis were 27Gy in 3 fractions which is more than the median dose used for extrahepatic lesions in Kato et al study but lower than 30Gy.

A study **by Kang et al. [25] o**bserved Response rate of 66.7% for portal vein tumour thrombosis treated by

SBRT alone and authors suggested that response rates of up to 73.5% could be achieved if combined with TACE (trans arterial chemo-embolization).

Another study conducted **by Goyal et al. [26]** involving unresectable liver tumours reported a 60% mean decrease in tumour volume three months post-treatment in case of HCC patients whereas a mean reduction in tumour volume of 59% was observed three months post treatment in case of liver metastases. Initial control rate was 82% with a median follow up of 8 months and three patients (two liver metastases patients and one patient with IHC) suffered from recurrences while seven patients experienced distant recurrences. The median **prescribed dose was 34Gy** (24-45Gy) in 1-3 fractions prescribed to median prescription isodose line of 70%. The study reported two grade 2 Gastrointestinal ulcers and one grade 3 GI ulcer. The authors concluded that CyberKnife Stereotactic Radiosurgery is successful local treatment for unresectable tumours of the liver.

Pancreatic tumour studies:

A study by song et al. [9] assessed the efficacy and safety of CyberKnife treatment for locally advanced pancreatic tumours (LAPC) and reported the median OS of 12.5 months and 1 year and 2 year survival rates of 53.9% and 35.1% respectively with one year freedom from local progression (FFLP) rate of 90.8% when treated with a **median dose of 45Gy (35Gy – 50Gy**) in 5 fractions. 61% of the patients experienced Grade 1-2 acute and late stage GI reactions where as one patient suffered from grade 3 toxicity. Multiplan Treatment planning system was used to create CyberKnife treatment plans and PTV was obtained by **adding a 3mm margin to GTV**. The **CK Synchrony motion tracking system** was used along with fiducial markers. The margins and dose reported in the song et al study are similar to the present case studies. Both respondents from US and Australia reported using 3-5 mm margin around GTV to obtain PTV for localized pancreatic cancer. Dose used in Australian institute was 40Gy in 5 fractions.

A study by Ji et al. [27] that compared CK SBRT plus Chemotherapy with Chemotherapy alone found that addition of SBRT improved local control rate (6 month PFS rate was 29.4% vs. 20.6% in CK+Chemotherapy and chemotherapy group alone)) but did not improve overall survival in patients with primary tumour of Liver only oligometastatic pancreatic cancer, primarily because many patients suffered from distant metastasis . There was no significant difference in the toxicity between the two groups.

PC studies:

A systematic review that assessed the clinical evidence of gantry versus robotic arm SBRT in prostate cancer patients concluded that neither device could be advocated for all prostate cancer patients [28]. However Robotic SBRT resulted in better or comparable freedom from biochemical failure for low and intermediate risk prostate cancer patients at 5-7 years. In terms of acute and late toxicities Robotic SBRT and Gantry based SBRT showed comparable results. The gantry based treatment resulted in grade 2 and greater GU toxicities that ranged from 5-8% vs. 4% -19.2% toxicity with Robotic SBRT. The GI grade 2 and greater toxicities in gantry based studies ranged from 7.5% - 8% vs. 0-12% in Robotic SBRT studies. while interpreting these results it is important to note that gantry based studies only had low risk patients and only 3 studies were reviewed whereas Robotic based studies included low, intermediate and high risk patients. The longer follow up and more extensive quality of life studies might change the reported toxicity percentages. The authors concluded that gantry based SBRT could be more useful for obese patients as higher energies could be used to treat these patients (greater than 6MV) and gantry based SBRT offers shorter treatment time per fraction compared to robotic SBRT [28]. The dose ranged from 33.5Gy to 40 Gy in 5 fractions in Gantry based studies and 32Gy-40Gy in 4-5 fractions in robotic SBRT studies.

Another study compared the CK plans with IMRT based techniques (VMAT, IMRT Sliding window, Helical Tomotherapy) for prostate cancer patients [29]. The study found no dosimetric differences in terms of PTV coverage and conformality but better PTV homogeneity was observed with rotational IMRT techniques at medium and high dose range. Bladder and rectum sparing was again better achieved with IMRT techniques than CK [29]. Helical Tomotherapy showed superior Normal Tissue Complication Probablity (NTCP) for rectum but no difference was observed for NTCP values for bladder with any of the techniques. **The target dose used in this study was 36.25Gy in 5 fractions over 1 week which is the same dose reported by professionals in the present study. As far as margins are concerned the present study results are in agreement with the margins used by Scobioala et al. [29]. In Scobioala et al. [29] study CTV included only Prostate (no Seminal vesicles) and to obtain PTV a 3mm margin was added in the dorsal direction (posteriorly) and a 5mm margin in ventral (Anteriorly) and lateral directions**.

Some researchers thinks CK may be associated with higher secondary malignancy rates due to a large volume of normal tissue receiving low dose radiotherapy along with longer treatment times and higher Monitor Units given by CK [30]. Researchers have suggested algorithms that can be used to reduce treatment delivery time by using beam angle class solutions for non coplanar SBRT with CK rather than using beam angle optimization for each individual patient [31].

A study by Rossi et al also showed superiority of Automatically generated CK robotic plans over manually

generated CK plans. AutoROBOT CK plans produced better rectal sparing than automatically generated VMAT plans [32].

Reasons behind CK adoption:

As far as reasons of CK adoption are concerned both experts agreed that CK was adopted to provide precise treatment delivery, to achieve better local control rates, to give re-treatment and to gain competitive edge in the clinical practice. The CK expert from Australia provided additional reasons for CK adoption namely dose escalation, reduce treatment time and for clinical research purposes. . A study by Brown et al.[6] showed that all NSCLC patients except one achieved at least partial response (30% reduction in tumour) and concluded that excellent control rates were achieved in early stage NSCLC patients when treated with CyberKnife.

A retrospective study conducted by Liu et al. [33] to evaluate safety and efficacy of CK treatment in 13 patients with olfactory groove meningiomas found 12 out of thirteen patients achieved 100% regional control rate at the time of follow up. There was a median tumour volume reduction of 31.7%. The study employed three dose regimes depending on tumour size i.e. 10Gy in 1fraction for tumours less than 10 cm^3, 25Gy in 5 fractions and 54Gy in 30 fractions for tumours greater than 10 cm^3 or in close vicinity of OARs. This study was conducted a medical centre in Boston, USA.

A study by Jereczek-Fossa et al. [8] found Actuarial 3 year in field progression free survival of 67.6%, Progression free survival of 18.4% and Overall survival of 31.2% in oligometastatic cancer patients treated with CK. The median dose was 24Gy in 3 fractions and complete radiological response was recorded in 17% of the lesions and partial response in 29% of the lesions. In 39% of the lesions the disease was found to be stabilized while in 15% of the lesions progressive disease was observed. The study concluded that CK treatment gives long term in-field tumour control with low toxicity.

A study by song et al. [9] showed median overall survival of 12.5 months in patients with locally advanced pancreatic cancer. 53.9 % of the patients had OS of one year whereas 35.1% of patients has a 2 year OS. The study reported 1 year freedom from local progression of 90.8%. This study treated patients with a median dose of 45Gy in 5 fractions whereas the prescribed dose ranged from 35-50Gy in 3-8 fractions. 90% of patients received Chemotherapy before or after CK treatment and grade 1-2 acute and late Gastrointestinal toxicity was reported in 61% of patients. In the present case study the most common dose regime used for pancreatic cancers was 40Gy in 5 fractions in Australian CK centre which is in line with the study by Song et al. [9].

A Case study conducted by **Accuray in St.Joseph's Hospital**, Phoneix, Arizon, US observed radiographically complete response in a patient suffering from $T1N_0$ M_0 NSCLC three months post treatment [34]. The patient had no surgery and was treated with 48Gy in 3 fractions (16Gy/fraction) while tumour motion was managed by CK Synchrony tracking system. A 5mm margin was added to GTV to get PTV. This study involved a radiation oncologist, a medical physicist and a Radiation therapist. This is in line with the present study as both respondents from US and Australia reported using a 5mm Margin to get PTV while planning CK treatment for lung cancer patients.

Another case study conducted by Accuray [35] in CyberKnife center of Miami, USA showed no evidence of disease 11 months post treatment with Fiducial free CK for T1N0M0 NSCLC. The patient was treated with 60Gy in 3 fractions (20Gy/Fraction) and motion was managed by XSight Lung tumour tracking system (Synchrony). The CK team in this case study included one radiation oncologist, one Thoracis Surgeon, two physicists, one dosimetrist and 2 therapists. The dose in the accuracy case study is similar to the dose usage reported by US CK expert in the present study for treatment of early stage Lung cancer.

CK Team composition

The data regarding number and type of CK team is mixed. However it seems that CK team must include at minimum a Medical Physicist, 2 Radiotherapy technologists and 1 radiation oncologist.

Tumour Tracking system

The present study has also showed that Synchrony system of CyberKnife is used in lung, pancreas, liver and kidney cancer patients for motion management in both Australia and USA. This is in agreement with the literature. A study by Nuyttens and Pol [36] showed CK synchrony system (4D rea time tumour tracking) can be used to treat moving tumours with 2mm accuracy while patients breathe normally.

CK Training Pathways

The present study has shown that in Australia SBRT symposium is used to gain CK knowledge and experience where as in USA the emphasis is on manufacturer's training programmes. No studies could be found that describe what strategies are used to gain CK Knowledge and experience in clinical and industry setting. The expert from the Australia also mentioned Experience as one of the ways to gain CK experience. Author of the

present study assumes that he meant probably in house training. Author of the current study recommend using other strategies to improve CK knowledge and experience of staff and radiation oncology students such as by offering Mentor based training, by designing and offering university courses that meet industry needs, by

offering practical hand on experiences in workshops, by encouraging oncology, medical physics and radiography related societies (e.g. ASCO, ESTRO, RTOG, APS, AAPM) to offer clinically relevant courses and workshops, by offering internships in Medical physics and by including physics and dosimetry in Undergraduate and post graduate syllabuses.

Future Directions

For future studies, author recommends doing similar studies but involving multiple institutes in USA, Australia, Europe and Asia to make data more generalizable and to gain more information on treatment induced toxicity, Local failure rates, overall survival, CK related organizational resources as well as on quality of life of cancer patients who have undergone CyberKnifetreatment

V. CONCLUSION

The present study consists of two comparative case studies and provides an overview of clinical, technical, organizational and Educational strategies and resources used by two institutes in USA and Australia to provide Stereotactic Radiosurgery and Stereotactic body Radiotherapy to cancer patients. The study captures the perspectives of two CyberKnife experts who have considerable experience of using CyberKnife.

As far **as clinical resources** are concerned the data regarding number and type of CyberKnife team is mixed. However it seems that CK team must include at minimum one Medical Physicist, two Radiotherapy technologists and 1 radiation oncologist. With respect to clinical treatment intent, CK is used to provide curative treatment in American institute and curative as well as palliative treatment in Australian institute. The study has shown CK is used for both intra and extra cranial tumours in both institutes in USA and Australia. In USA CK is used for only early stage disease whereas it is used for both early and advanced stage cancers in Australian institute.

In terms of **technical resources**, CyberKnife Multiplan Treatment planning system is used by Medical physicists to create CK treatment plan in US institute whereas Accuray Precision Radiotherapy TPS are used by Radiation technologists to create CK treatment plans in Australian institute. The study has shown that In room volumetric imaging, CyberKnife tracking system (6D Skull, Fiducial, X Sight spine with Synchrony, X Sight lung with Synchrony and Fiducials) and planar imaging are used before and during the treatment to localize and verify the target based on various sites. In US institute, Fiducial markers are not used for brain, spine and most lung tumours. In terms of immobilization devices mask for c-spine and brain tumours are used in US institute and headframe are used during treatment of brain tumours in Australian institute.

In the present study Different doses were reported for lung cancers by both experts (60 Gy in 3-5# in USA vs. 54Gy in 3# Australia). Most common dose was spinal cord tumours was 27Gy in 3 fractions, for liver tumours 45 Gy - 54 Gy in 3 fractions, for prostate cancer was 35-36Gy in 5 fractions and for pancreatic tumours 40Gy in 5 fractions. In the present study fatigue and tiredness were most common acute toxicity experienced by patients suffering from prostate, liver, pancreas and kidney cancers.

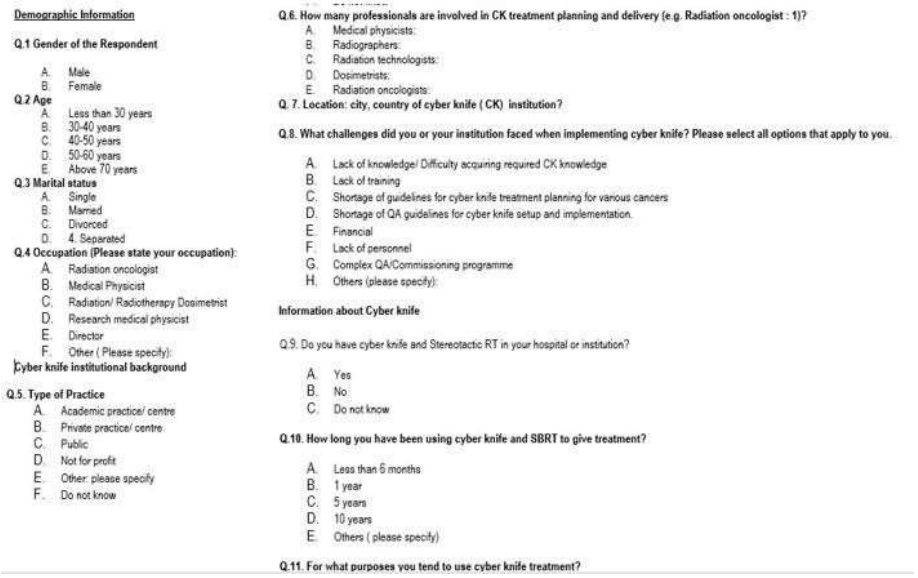
In the present study zero margin was added to GTV to obtain CTV for **localized prostate disease** and a margin of 3mm posteriorly and 5mm anteriorly and laterally was added to obtain PTV. Both respondents from US and Australia reported using 3-5 mm margin around GTV to obtain PTV for **localized pancreatic cancer. In the present case studies a margin of 2mm was added to achieve PTV for spinal metastases in USA case study and a margin of zero in Australian case study. A margin of 5mm was reported in both** case studies for liver metastasis.

Under the category of CK organizational resources and strategies, the present study found challenges faced during CK implementation in the organization and reasons for CK adoption. As far as reasons of CK adoption are concerned both experts agreed that CK was adopted to provide precise treatment delivery, to achieve better local control rates, to give re-treatment and to gain competitive edge in the clinical practice. The CK expert from Australia provided additional reasons for CK adoption namely dose escalation, reduce treatment time and for clinical research purposes. In the present study, the respondent from Australia said they experienced financial difficulties while respondent from US said they experienced no challenges in implementing CK in the institute. Both CK experts found CK technology cost effective compared to VMAT, IMRT and Tomotherapy. From the perspectives of US CK expert, CK provides better tumour control, DFS, OS and reduced treatment induced toxicities compared to IMRT,VMAT and proton therapy.

To ensure accurate and efficient CK implementation, treatment planning, delivery and Quality assurance staff must be well educated. The present study has shown that in Australia SBRT symposium is used to gain CK knowledge and experience where as in USA the emphasis is on manufacturer's training programmes.

The study also found that In USA Radiation oncology and medical physics programmes provide SBRT and CK experience whereas according to CK expert in Australian institute oncology and medical physics programmes do not provide SBRT and CK experience.

Appendix A: A sample CyberKnife E- Survey 2020



Demographic Information

Q.1 Gender of the Respondent

A. Male
B. Female

Q.2 Age

A. Less than 30 years
B. 30-40 years
C. 40-50 years
D. 50-60 years
E. Above 70 years

Q.3 Marital status

A. Single
B. Married
C. Divorced
D. 4. Separated

Q.4 Occupation (Please state your occupation):

A. Radiation oncologist
B. Medical Physicist
C. Radiation/ Radiotherapy Dosimetrist
D. Research medical physicist
E. Director
F. Other (Please specify):

Cyber knife institutional background

Q.5. Type of Practice

A. Academic practice/ centre
B. Private practice/ centre
C. Public
D. Not for profit
E. Other: please specify
F. Do not know

Q.6. How many professionals are involved in CK treatment planning and delivery (e.g. Radiation oncologist : 1)?

A. Medical physicists:
B. Radiographers:
C. Radiation technologists:
D. Dosimetrists:
E. Radiation oncologists:

Q. 7. Location: city, country of cyber knife (CK) institution?

Q.8. What challenges did you or your institution faced when implementing cyber knife? Please select all options that apply to you.

A. Lack of knowledge/ Difficulty acquiring required CK knowledge
B. Lack of training
C. Shortage of guidelines for cyber knife treatment planning for various cancers
D. Shortage of QA guidelines for cyber knife setup and implementation.
E. Financial
F. Lack of personnel
G. Complex QA/Commissioning programme
H. Others (please specify):

Information about Cyber knife

Q.9. Do you have cyber knife and Stereotactic RT in your hospital or institution?

A. Yes
B. No
C. Do not know

Q.10. How long you have been using cyber knife and SBRT to give treatment?

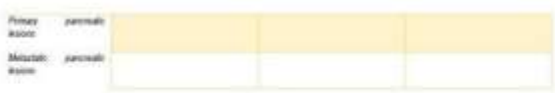
A. Less than 6 months
B. 1 year
C. 5 years
D. 10 years
E. Others (please specify)

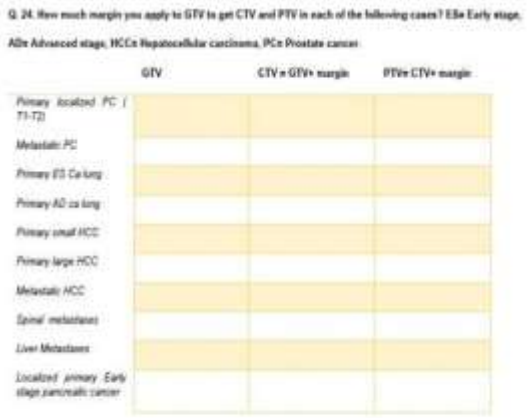
Q.11. For what purposes you tend to use cyber knife treatment?

Q. 10. What type of image guidance you use to localize target / verify target before each cyber knife treatment?

Select all that apply

- In room volumetric imaging (e.g. cone beam CT)
- In room Planar imaging
- Both in room volumetric and planar imaging
- CK image guidance system
- Fiducial markers
- SBF to establish an external co ordinate system
- Other: please specify
- Do not know




Q. 24. How much margin you apply to GTV to get CTV and PTV in each of the following cases? ESe Early stage,
ADe Advanced stage, HCCn Hepatocellular carcinoma, PCn Prostate cancer

	GTV	CTV = GTV+ margin	PTV= CTV+ margin
Primary localized PC (T1-T2)			
Metastatic PC			
Primary ES Ca lung			
Primary AD ca lung			
Primary small HCC			
Primary large HCC			
Metastatic HCC			
Spinal metastases			
Liver Metastases			
Localized primary Early stage pancreatic cancer			

Q. 25. What Energy of Linac you use to treat following diseases when using CK?

Q.26. Which treatment planning systems you use to create radiation plans for Cyber knife?
A. Multiplan treatment planning system
B. Pinnacle
C. Eclipse
D. Other (Please specify)

Q. 27. Who carries out CK radiation treatment planning in your organization?
A. Medical Physicists
B. Radiographers
C. Radiation technologists
D. Radiation Dosimetrists
E. Physics Assistant

Q.28. Which type of techniquse you aregley to control breathing induced motion?

	Ca Lung	Ca PC	Ca pancreas	Ca liver	Ca kidney
Fiducial markers					
Respiratory gating					
Abdominal compression					
Real time tumour tracking					
CK system (Synchrony Respiratory tracking system)					
Breath hold techniques					
Other (Please specify)					

Q. 29 What most common acute toxicities patients experience (up to 3 months) after receiving CK treatment in each case:

	Ca lung	Ca PC	Ca liver	Ca Pancreas	Ca kidney	Spinal ca
Dyspnea						
Pneumonitis						
Diarrhea						
Other Bowel problems						
Bladder problems						
Fatigue & Tiredness						
Pain						
Appetite loss						

Knowledge and Experience:

Q.30. How did you and other team members in your organization gain the required CK and SBRT knowledge and experience?

A. Manufacturer training programme
B. SBRT symposium
C. University courses
D. Other: (Please specify)

Q. 31. Are radiation oncology and medical physics programs in your country provide experience in SBRT and CK?

Q.32. Is CK treatment cost effective compared to other Radiation therapy technologies such as VMAT, IMRT, Tomotherapy?

Q.33 For which cancers CK treatment provides better tumour control, disease free survival and overall survival and reduced treatment induced morbidity compared to IMRT, VMAT and proton therapy?

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