Head and neck tumors
(Primary and metastatic tumors of buccal space, pharynx and larynx, nasopharynx cancer, schwannoma, recurrences)

Cancerous or non-cancerous intracranial tumors
(Brain metastases, meningiomas, neurinomas, gliomas, astrocytomas, pituitary adenomas, vestibular schwannomas, trigeminal neuralgia, arteriovenous malformations)

Breast cancer

Liver cancer
(Inoperable primary liver cancer, metastases)

Lung cancer
(Early stage lung cancer, pulmonary metastases, recurrences)

Pancreas cancer
(Inoperable patients, recurrences)

Spine cancer
(Benign tumors, spinal metastases, primary malignant tumors, spinal AVMs)

Prostate cancer
(Low and intermediate risk prostate cancer, high risk prostate cancer, recurrences)

Osseous metastases

Liver cancer
(Inoperable primary liver cancer, metastases)
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**Kilby et al., The CyberKnife® Robotic Radiosurgery System in 2010.**
Tech in Cancer Research & Therapy, 2010 (Accuray)

- Lead article in new special issue of TCRT
- A complete technical description of the CyberKnife® VSI™ System
- First complete technical review of system since the late 1990s
- Updates technical advancements of the CyberKnife System
- Includes detailed review of studies of geometric accuracy
- Relation of technical developments to expansion of clinical applications is reviewed
- Open access makes it freely available to anyone with internet access:
Primary / Metastatic Cancers


The introduction of the CyberKnife extended the indication to 63 patients (30%) who could not have been treated by single-session radiosurgical techniques.

- All patients were either symptomatic or harbored growing tumors
- In 150 patients with lesions larger than 8 mL or with tumors situated close to critical structures, the dose was delivered in 2 to 5 daily fractions
- The tumor volume was unchanged in 148 patients, decreased in 36 patients and increased in 7 patients
- 93.4% control rate at 5 year follow up


Functional Disease


Examined clinical outcomes in TN patients who underwent lesioning with “optimized” nonisocentric radiosurgical parameters.

- 6-mm segment of nerve was treated with a marginal prescription dose of 58.3 Gy and a maximal dose of 73.5 Gy
- At a mean follow-up of 14.7 months, patient-rated outcomes were:
  - excellent in 33 patients (72%)
  - good in 11 patients (24%)
  - poor/no improvement in 2 patients (4%)

Facial numbness was reported in 7 patients (15%).

Target: Elongated segment of the retrogasserian cisternal portion of the trigeminal sensory root


CyberKnife treatment planning allowed use of functional MRI and angiograms to help accurately delineate the AVMs and critical structures.

- 279 AVM patients treated with CyberKnife® System
- AVM volumes ranged from 0.1 to 42 cc
- Delivered dose 22.5-30 Gy, mostly single fraction
- Follow-up (median): 31 months; 80 patients with 36+ months
- Excellent Toxicity Outcomes:
  - No permanent complications, even though 20 patients had AVMs next to critical structures
  - Efficacy Outcomes:
    - High rate AVM obliteration: complete AVM obliteration in 81.2% patients at 36 months
    - 91% complete obliteration in small AVMs
    - Low interim bleeding rate observed
- Obliteration rates were significantly better than their previous LINAC-based results
- Use of functional MRI and angiograms to accurately delineate AVMs and critical structures

Versus Gamma Knife


The radiosurgical dose can be better tailored to the target with the CK than with the GK. This result, a more homogeneous dose distribution, and a lower peripheral dose represent an advantage of the CyberKnife in regard of the radiation protection.

- Retrospective matched-pair analysis of 2 groups of 63 patients: All treated in a single fraction either with Gamma Knife® (GK) or CyberKnife® System (CK)
- Minimum marginal dose was significantly different
  - 19.4 ± 2.5 Gy for GK and 18.4 ± 1.5 Gy for CK
  - Central tumor dose was also lower for CK
- Conformality, homogeneity, and volume of non-tumor tissue receiving 10 Gy or more were significantly better for CyberKnife treatment plans
- Clinical outcomes were nearly identical between groups
  - Local control at 12-18 months was 94.6% for GK and 93.8% for CK

**Accuracy**

Antypas C, Pantelis E. Performance evaluation of a CyberKnife® G4 image-guided robotic stereotactic radiosurgery system.

Fu D, Kuduvalli G. A fast, accurate, and automatic 2D-3D image registration for image-guided cranial radiosurgery.


**Treatment plans**

Radiat Oncol 2006;1:46.


**Intrafraction motion**


Murphy MJ. Intrafraction geometric uncertainties in frameless image-guided radiosurgery.


**CyberKnife® System Accuracy: Intracranial**

Total system error
- Scan, plan, irradiate, compare computed and measured dose distributions
- Includes all sources of delivery error: imaging, image transfer, planning, tracking, robot, linac

6D Skull tracking
- Relies on intrafraction imaging to continually assess target movement
- Total clinical accuracy of about 0.50 mm
  - 0.44 +/- 0.12 mm, Antypas et al. 2008
  - 0.34 +/- 0.16 mm for a target 2 cm from the rotation center, Fu et al. 2008
  - 0.48 +/- 0.22 mm, Muacevic et al. 2009

**HEAD AND NECK**

**Clinical papers**


Metastases


- 200 patients with 274 primary and metastatic spinal tumors
- 76% of patients reported pain at the tumor site before treatment
- CyberKnife® treatment mean dose 26.4 Gy in 3 fractions

- 1 month after treatment:
  - Pain scores had decreased significantly after treatment and decreased over the entire 4-year follow-up period
  - 38% of the patients reported that they were completely pain-free
- Significant continued improvement over 48 months follow-up
- Physical Quality of Life (QOL) were not reduced by SRS; Mental QOL improved
- Side effects were mild and self-limited, and no late radiation toxicity was observed
- Patients with the worst initial pain showed the most improvement

SRS of metastatic and primary spinal tumors with the CyberKnife results in robust and durable improvement in pain and maintenance of the physical and mental quality of life


A prospective non-randomized longitudinal cohort study
- Maximum single-fraction doses of 12.5 to 25 Gy (mean 20 Gy)
- Long-term pain improvement occurred in 290 of 336 cases (86%) treated for pain indication
- Radiographic control:
  - 90% long term tumor control for cases treated with radiosurgery as primary modality
  - 88% tumor control for previously treated lesions
- Clinical improvement in 84% of the cases with pre-treatment neurological deficits
- No case of radiation-induced myelitis

Conclusions
Single-fraction spinal CyberKnife® stereotactic radiosurgery for metastases is both safe and clinically effective.

Furwege et al. Patient motion and targeting accuracy in robotic spinal radiosurgery: 260 single-fraction fiducial-free cases.

- Clinical patient data were used to evaluate the tracking performance of the algorithm and quality assurance
- 77 spine patients treated with the CyberKnife® System
  - 51 patients treated using Xsight® Spine Tracking (no fiducials)
  - 26 patients treated using fiducial tracking
  - 10,522 X-ray image pairs
- Collected under many technical and clinical conditions
  - Using G3 (short stands) or G4 (in-floor and on-floor detectors)
  - All spine regions
  - Wide range of patient sizes
  - Clinical conditions included osteoporosis and implanted surgical hardware (cages, rods & screws)

- Overall median targeting error 0.48 mm


Primary lesions / AVMs

Neurosurgery 2006;58:674-685; discussion 674-685.

Neurosurgery 2006;58:1081-1089; discussion 1081-1089.

Xsight® Spine accuracy

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Neurosurgery 2006;58:674-685; discussion 674-685.

Neurosurgery 2006;58:1081-1089; discussion 1081-1089.
Primary, metastases, recurrences


Primary and metastatic central lung tumors

This study is important for the CyberKnife differentiation strategy. It shows that the Synchrony Respiratory Tracking System allows narrow PTV margins, so that high SBRT doses can be delivered with relatively low toxicity to the central chest region, where SBRT has been shown to carry a high risk of serious complications, including death, within 2 cm of the primary central airways of the lung.

- 56 patients (39 with primary NSCLC, 17 with solitary metastases) with 58 tumors in the central chest
- Median tumor diameter was 4.1 cm (range 1.2–10.5 cm)
- Synchrony motion tracking & automatic correction allowed narrow margins (5 mm GTV to PTV)
- Near-esophagus tumors treated with 6 fractions of 8 Gy to 60 Gy (in 3 fractions)
- Disease control: 2-year local control 97%; overall survival 90%
- Toxicity
  - No acute or late grade 4 or 5 toxicity
  - Low-grade esophagitis in 11% of patients
  - “Toxicity amongst lowest reported to date” for central lesions

Key Points
- “Two-year tumor control and overall survival have been comparable to that generally reported for SBRT of peripheral NSCLC lesions for patients treated to BED = 100 Gy, and toxicity has been among the lowest reported for central lesions”

Quality of Life

- Aggressive treatment for octogenarians?
  - With palliative treatment only, most patients die of the disease
  - 5-year survival post-surgery is 34%-57%, but surgery is hard on patients
  - SBRT may be a less invasive approach to curative treatment
- 38 patients 80+ years of age were treated with 45-60 Gy in 3-6 fractions (more fractions for central and large tumors)
- Toxicity
  - 5% acute, 16% late Grade 3 tox (temporary chest pain, shortness of breath)
- Outcomes at 23 months’ median follow-up
  - 2-year local control 100%
  - Overall survival 65% at 1 year, 44% at 2 years (90% for T1 tumors)


- N/dose: 39 pts with inoperable T1/2 NSCLC / 48-60 Gy in 3-5 fx
- Follow-up: 17 months median
- Disease control: 2-year local control 97%; overall survival 82%; QOL maintained or improved
- Late toxicity: Low-grade fatigue and dyspnea in some / chest wall pain in 2 pts

Key Points
- Goal of study was to assess quality of life (QOL) after CyberKnife® treatment of inoperable NSCLC
- No severe toxicity in 6 patients with central lung tumors
- COPD symptoms not worsened by SBRT
- High rate of 2-year local control
- Preservation of physical QOL, improved emotional QOL


- 87% overall survival at 2 years
- 100% local control at 2 years
- 87% overall survival at 2 years


- Primary and metastases, recurrences
- At median follow-up of 23 months
  - 2-year local tumor control was 76% for all tumors
  - 85% for BED >100 Gy
  - 60% for BED <100 Gy
  - Overall 2-year survival 60%
- Three-year cancer-specific survival 80% for patients with early stage I NSCLC and 58% for patients with metastases
Synchrony® tracking in phantoms


Tracking model error minimal in clinical use


4D planning does not encompass all movement


Image-guided RT needs to involve real-time verification of tumor position during treatment delivery for optimal RT treatment outcomes

- Assessed 4D-CT use for accurately predicting intra-fraction motion of pancreatic tumors.
- Pancreatic tumor motion likely similar to tumors in the lower lobes of the lungs.

- Motion as indicated in pre-treatment 4D-CT was compared to tumor motion shown in Synchrony® tracking logs for 20 patients treated with the CyberKnife® System.

4D-CT predicted motion in SI and AP directions (with error), not in LR direction.
- A single 4D-CT may not be sufficient to predict organ movement caused by patient respiratory motion during an actual course of treatment.
- In 16/20 patients, if 4D-CT was only used to model motion, >10% of tumor motion would be missed during treatment.
- Clinical implications of this error may be decreased tumor control rates and increased normal tissue toxicity.

Monte Carlo dose calculation


Key Points

- Compared of lung dose distributions calculated by Ray-Tracing (EPL) and Monte Carlo (MC) algorithms.
- 33 patients were treated to 30-60 Gy prescribed to an isodose line to obtain 95% target coverage.
- EPL consistently overestimated doses; median ratio of EPL to MC max dose was 1.16 (range, 1.1-1.63).
- Discrepancy was greatest in cases where beams crossed long low-density tissue.
- Doses to critical structures such as spinal cord, heart, and esophagus were overestimated by 1-2 Gy.
- Authors recommend using MC to calculate all lung SBRT dose distributions.

BREAST


- Review of partial breast irradiation, a hypofractionated radiotherapy technique for treatment of breast tumor resection cavities. Similar CyberKnife treatment approaches are under consideration.

Evaluates CyberKnife® dose plans for partial breast irradiation (PBI) of early stage breast cancer

Heinzerling et al. #3390 (Bob Timmerman, Senior Author) U Texas Southwest - Comparative Dose-Volume Analysis for CyberKnife and 3D Conformal Partial Breast Irradiation Treatment of Early Stage Breast Cancer

- Plan dose/ fx : 34 Gy in 10 fx for CK and 3D CRT (15 mm margin, less near skin & chest).
- OAR doses : Dose to lung, heart, normal breast lower with CK, skin doses not sig. different.
- 10 patients with clearly delineated lumpectomy cavities were re-planned.
- 3D CRT treatment plans used 4-5 non-coplanar beams.

Outcomes

- CTV coverage was superior for CyberKnife (Median 98% for CK, 95% for 3D CRT).
- Doses outside the PTV were significantly lower with CyberKnife.

Conclusions

- "When the advantages of CK to account for target motion and setup error are considered, CK would even further reduce dose to OARs."
- "Reduction in dose to the normal breast seen with the CK system may translate into better cosmetic outcomes and is currently being evaluated in a phase I trial at our institution."

- 42 patients: 62 metastases, were treated with two dose levels of 40 Gy in four Dose per Fraction (23) and 45 Gy in three Dose per Fraction (13)
- Disease control: 1-year local control 90%; 2-year local control 86%; overall survival 90%
- Toxicity : Grade 1 or 2 nausea, one patient Grade 3 epidermitis
- Follow up (median): 14.3 months

**Key Points:**
- No significant difference between 40 and 45 Gy
- Better local control with the higher dose
- Combined a local treatment with chemotherapy
- Cases of toxicity milder than those reported in the literature for SIRT treatments
- Treatment with 45 Gy seemed to increase local control without additional toxicity.


- 27 patients with unresectable liver metastases were included in these series
- Patients were treated with a median dose of 36 Gy (range 25-60 Gy) in 3 fractions
- Median follow up was 13 months (range, 6-16 months)
- Overall tumor control was 74.1% (inhibition of growth or reduction in size)
- Mild or moderate transient hepatic dysfunction was evident in 9 patients and minor complications in 5

**Key Points:**
- Patients ineligible for any other treatment mode (Child A5—B9); all inoperable, poor-prognosis patients
- Short-lived mild hepatic pain, nausea, fatigue in 48% at 3 months
- Grade 2 (2 pts) and 3 (1 pt) duodenal ulcer in early patients who exceeded dose constraints
- Local control superior to other studies, survival comparable
- A multicenter Phase II study funded by French NCI is planned


**Key Points:**
- 26 patients: 19 metastases, 5 IHCC, 2 recurrent HCC
- Dose-escalated from 18 to 30 Gy in a single fraction
- Median follow-up: 17.3 months (range, 2-35 months)
  - At 12 months, risk of local failure 23%
  - Median survival: 26.6 months
  - Overall 2-year actuarial survival 50.4%
  - Mets: 49.4%; Primary: 53.6%
- Toxicity - No Grade 3 or higher toxicity
  - Acute: 3.8% Grade 2
  - Late: 7.7% Grade 2
- No dose-limiting toxicity
- Good local control and survival, minimal acute and long-term toxicity


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PROSTATE

Clinical papers

Freeman & King. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiation Oncology 2011

Key Points:
- First of CyberKnife® treatment of prostate that includes 5-year follow-up
- Combined data from Naples (35 Gy) and Stanford (36.25 Gy)
- 5-year disease-free survival 93% (within range of other treatments)
- Generally low rates of mild GU and GI toxicity (within range of other treatments)
- "SBRT may benefit patients by reducing travel costs and lost work time, allowing a more immediate return to normal daily routines, and potentially reducing health care costs"


Efficacy of CyberKnife® Prostate Radiosurgery

- CyberKnife® hypofractionation has "early and late toxicity profile no worse than with dose-escalated radiotherapy delivered at conventional fractionation"
- 41 patients treated in 5 fractions of 7.25 Gy
- 100% PSA response rate at median of 33 months
- Urethral/rectal toxicity profile comparable to EBRT


Key Points:
- 22 low-risk, 23 intermediate-risk (17 received ADT)
- Patients were of an "advanced age" and were deemed "ineligible for surgery"
- Grade 3 urinary toxicity occurred in a former TURP patient
- Neither prostate volume nor ADT status affected toxicity
- Second European addition to the prostate SBRT evidence base


Key Points:
- 97% biochemical control at median 24 months
- Urethral/rectal toxicity profile comparable to EBRT
- Erectile function preserved in 81% of patients at 2 years
- "EF preservation for open surgery and conventional radiation therapy ranges from 50-70 percent"

Technical papers


The advantage of using the Calypso system for real-time prostate tracking, to improve accuracy by a few millimeters, is diminished in comparison to the loss of MRI/MRS options for more accurate post-treatment follow-up and monitoring

- Studied Calypso system with phantom and patients at each stage of treatment
- Assessed whether transponders were displaced or heated by MRI, and whether they caused image artifacts on MRI
- Large artifacts were visible on MRI
- "Calypso transponders will hinder the use of pelvic MRI/MRS for follow-up studies, limiting assessment options for the physician and the patients."