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Is it cost-effective to treat brain metastasis with advanced technology?

Cost-effectiveness analysis of whole brain RT, stereotactic radiosurgery and craniotomy in HA setting

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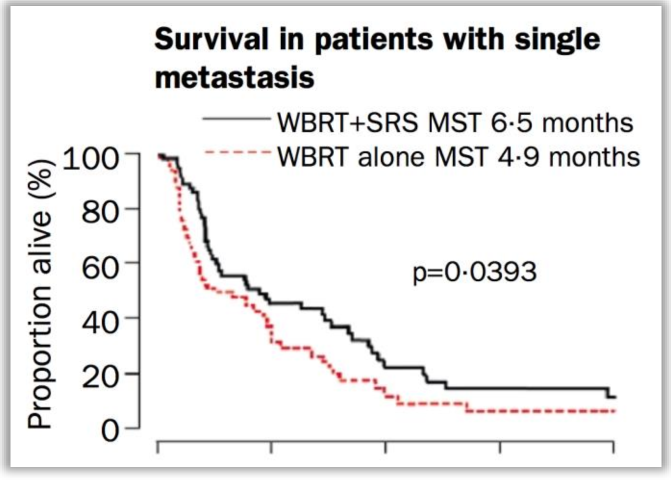
Background

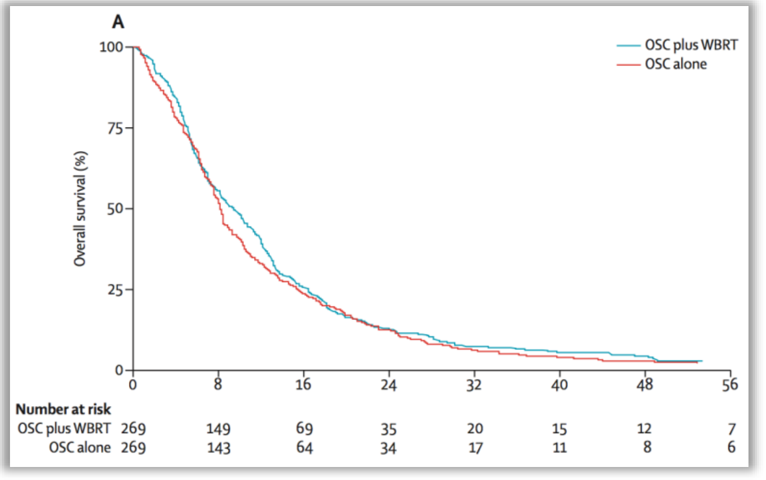
- Brain metastases occurred in 30% of patients with advanced cancer
- Uncontrolled brain metastases may cause debilitating symptoms including seizure and hemiplegia, which may result in prolonged hospitalization and huge social costs
- Whole brain radiation therapy (WBRT) has been applied extensively in Hospital Authority for decades
- In recent years multiple RCTs had confirmed the superior disease control and neuro-cognitive function preservation by stereotactic radiosurgery, albeit at a higher cost and complexity

Whole Brain Radiation Therapy (WBRT)
The Insufficiency

- No RCT has ever showed the survival benefit of WBRT alone for brain metastases
- For in-operable brain met in lung cancer patients, median overall survival of WBRT alone was around 9 weeks only (QUARTZ, Lancet 2016). No benefit versus steroid alone
- Tuen Mun Hospital audit: WBRT alone - median survival 7-8 weeks only
- Impairment of QoL and neurocognitive function, esp in the first 3 months
- ***WBRT is "inexpensive" from patients' perspective, but the societal cost and health care cost of poorly controlled brain met is high!***



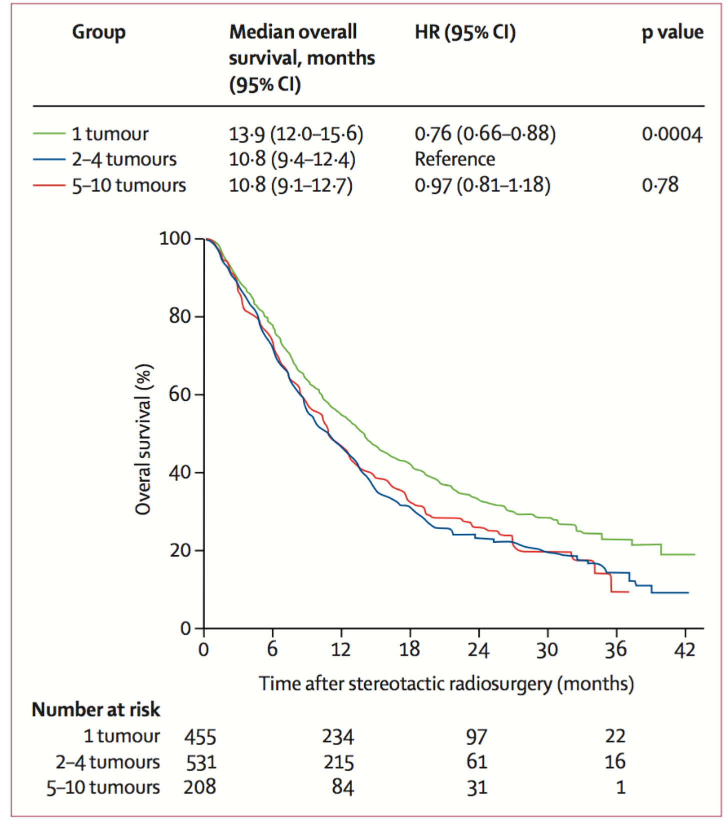
RTOG 9508. WBRT vs WBRT + SRS. Lancet 2004



QUARTZ study. WBRT vs steroid alone. Lancet 2016

Stereotactic Radiosurgery (SRS)
A delux treatment?

- SRS alone compared with WBRT alone
  - Better local control
  - Better QoL and neurocognitive function
  - Higher chance of “distant” CNS recurrence
  - Need frequent surveillance MRIs and system being capable to provide early salvage treatment (SRS/craniotomy/WBRT)
  - Technically more demanding. Much more input from oncologists, dosimetrists and medical physicists
  - Small but significant risk of radiation necrosis
- “Number of metastases” is no longer a limitation
  - Multiple brain metastases (up to 10) patients are suitable for SRS



JLGK0901, prospective cohort study of 1-10 brain metastases
Lancet Oncology 2014

Clinical question

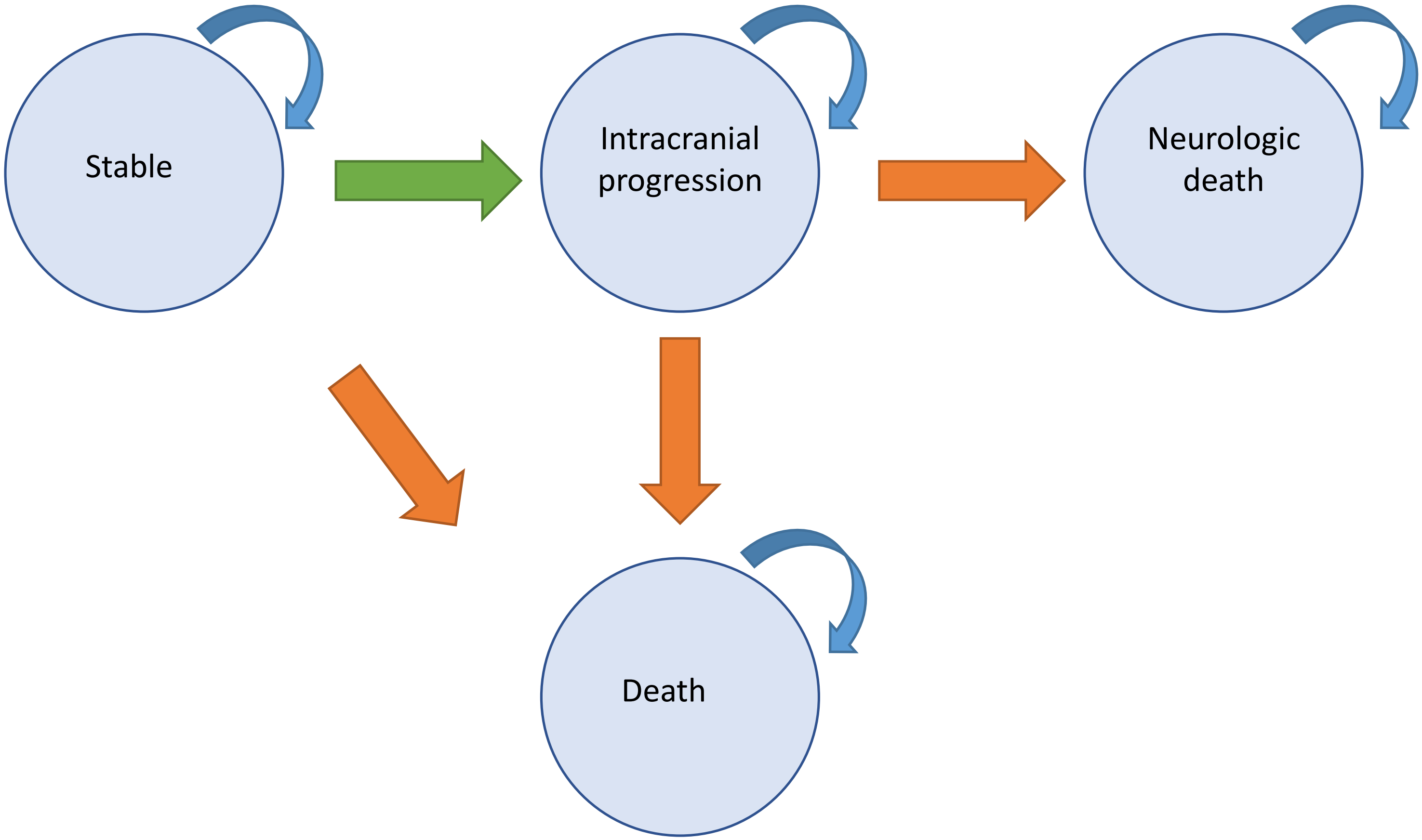
- Is SRS alone cost-effective compared with WBRT alone in Hong Kong (HA) setting?

- How about comparing SRS versus craniotomy?

Cost effectiveness analysis
Methodology

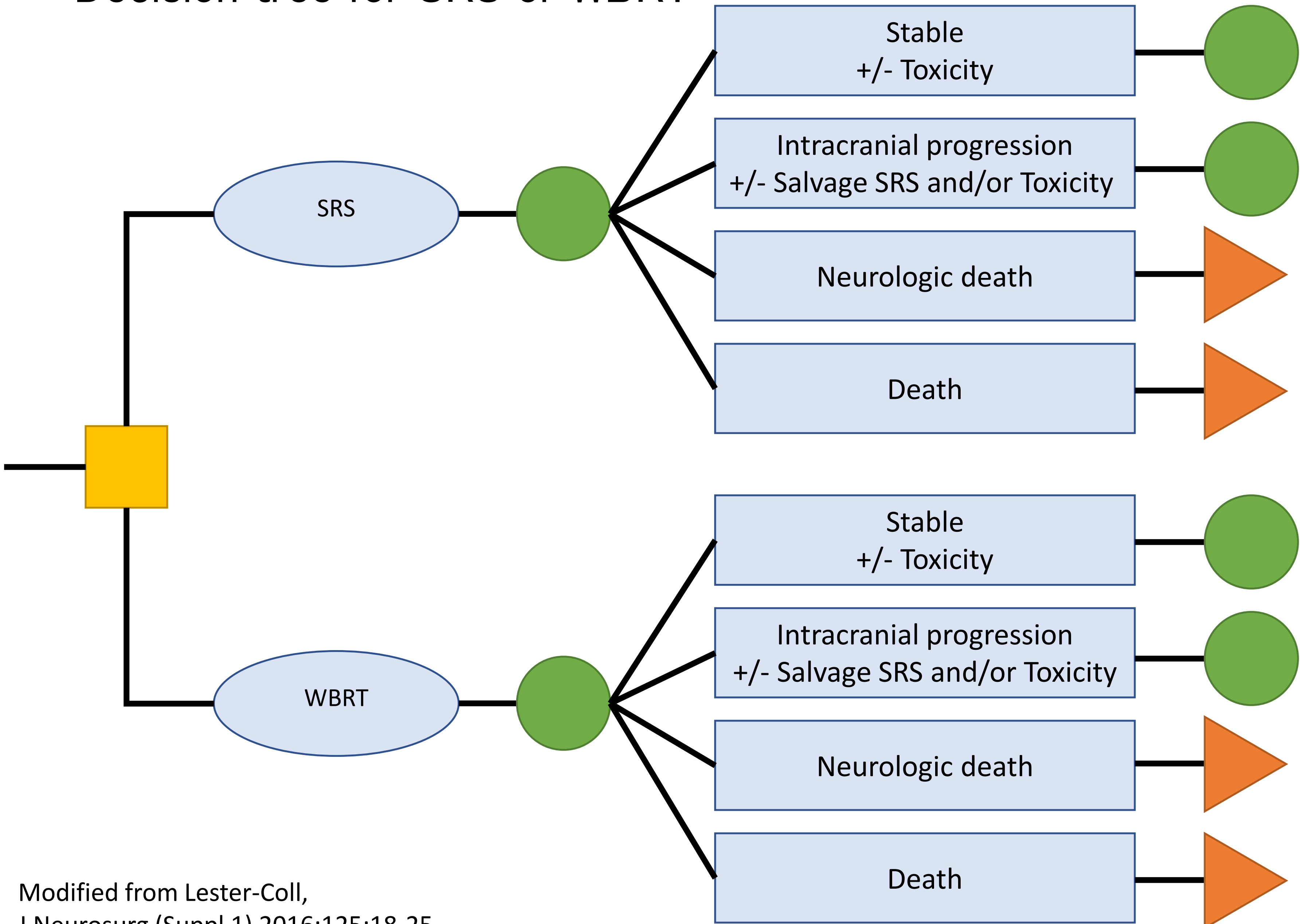
- A state transition Markov model was constructed
- Patients entered the model at diagnosis of brain metastases and exited at the time of death from cancer.
- The cycle length was 1 month, and the model was run for 24 consecutive months.

Markov Model – 3-state disease model



Modified from Lester-Coll,
J Neurosurg (Suppl 1) 2016;125:18-25

Decision tree for SRS or WBRT



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Cost effectiveness analysis
Methodology – transitions probabilities

- SRS alone arm
  - The rates of local control, intracranial failure, neurocognitive decline, radiation necrosis and salvage SRS (33%-43%) for the patients treated with SRS alone were estimated form the report of JLGK0901.
- WBRT arm:
  - The rates of local control, intracranial failure, neurocognitive decline, and salvage SRS for the patients treated with WBRT alone were estimated form the report of Radiation Therapy Oncology Group (RTOG) 9508 and EORTC 22952–26001 trials

TABLE 1. Model parameters and assumptions

Variable	Base Case & Range for sensitivity analysis	Authors & Year
Transition probabilities		
Progression from stable state		Yamamoto et al., 2014
1 brain metastasis	0.016 (0.012–0.020)	
2–10 brain metastases	0.029 (0.022–0.036)	
Death from stable state		Yamamoto et al., 2014
1 brain metastasis	0.040 (0.030–0.050)	
2–10 brain metastases	0.059 (0.044–0.073)	
Death from progression state		Yamamoto et al., 2014
1 brain metastasis	0.078 (0.059–0.098)	
2–10 brain metastases	0.045 (0.034–0.057)	
Salvage SRS		Yamamoto et al., 2014
1 brain metastasis	0.33 (0.24–0.41)	
2–10 brain metastases	0.43 (0.32–0.54)	
Neurological death		Yamamoto et al., 2014
1 brain metastasis	0.10 (0.075–0.13)	
2–10 brain metastases	0.04 (0.03–0.05)	
Probability of neurocognitive decline		Yamamoto et al., 2014
1 brain metastasis	0.004 (0.003–0.005)	
2–10 brain metastases	0.004 (0.003–0.005)	
Probability of radionecrosis	0.001 (0.00075–0.0013)	Yamamoto et al., 2014
Hazard ratio (HR) for impact of SRS boost on local control	1.20 (0.60–1)	Andrews et al., 2004
Hazard ratios (HR) for impact of WBRT on outcomes		
Intracranial failure	0.61 (0.46–0.77)	Kocher et al., 2011
Salvage SRS	0.31 (0.23–0.39)	Kocher et al., 2011
Neurocognitive decline	1.55 (1.16–1.94)	Kocher et al., 2011
Health utilities		
Stable after SRS	0.85 (0.75–0.90)	Lester-Coll et al., 2016[17]
Stable after WBRT	0.70 (0.50–0.80)	Lester-Coll et al., 2016[17]
Progression	0.55 (0.45–0.65)	Lester-Coll et al., 2016[17]
Neurological death	0.25 (0.15–0.30)	Lester-Coll et al., 2016[17]
Radionecrosis	0.50 (0.40–0.60)	Lester-Coll et al., 2016[17]
Neurocognitive decline	0.30 (0.20–0.40)	Lester-Coll et al., 2016[17]

Modified from Lester-Coll, J Neurosurg (Suppl 1) 2016;125:18-25

Cost effectiveness analysis
Methodology – cost break-down

			HK$
SRS	Moulding	$5,510	$124,700
	CT simulation	$7,500	
	MRI simulation	$5,000	
	SRS computer planning	$34,600	
	Target localization	$30,000	
	Quality assurance	$2,740	
	Treatment (1 fraction)	$39,350	

WBRT	Moulding	$4,000	$63,760
	Conventional simulation	$2,360	
	Computer 2D planning	$5,660	
	Target localization	$15,000	
	Quality assurance	$2,740	
	Treatment (10 fractions)	$30,000	
	Treatment verification (x2)	$4,000	

			HK$
Craniotomy	Ultra-major II	$100,000	$176,820
	Deep sedation	$13,720	
	Pathology	$3,000	
	Intensive care unit (1 day)	$24,400	
	Inpatient stay (7 days)	$35,700	

MRI with contrast		$5,000	$5,000

Progression	Admission (3 days acute ward, 5 days convalescence ward)	$22,000	$23,230
	AED visit (x1)	$1,230	
	CT brain		
	Blood tests		

Death	Hospice stay (14 days)	$18,760	$97,780
	General ward stay (14 days)	$71,400	
	AED visit x2	$2,460	
	SOPD visit x4	$5,160	

Cost effectiveness analysis
Methodology – primary endpoint

- Quality-adjusted life year **(QALY)**
- Incremental cost-effectiveness ratios **(ICERs)**—the difference in costs divided by the difference in effectiveness between 2 treatment arms
- Willingness-to-pay threshold
  - GDP per capita of Hong Kong in 2017: HK$360,220
  - International mean: 200% of GDP per capita*

*Khachapon Nimdet, et al. PLOS Apr 2015.

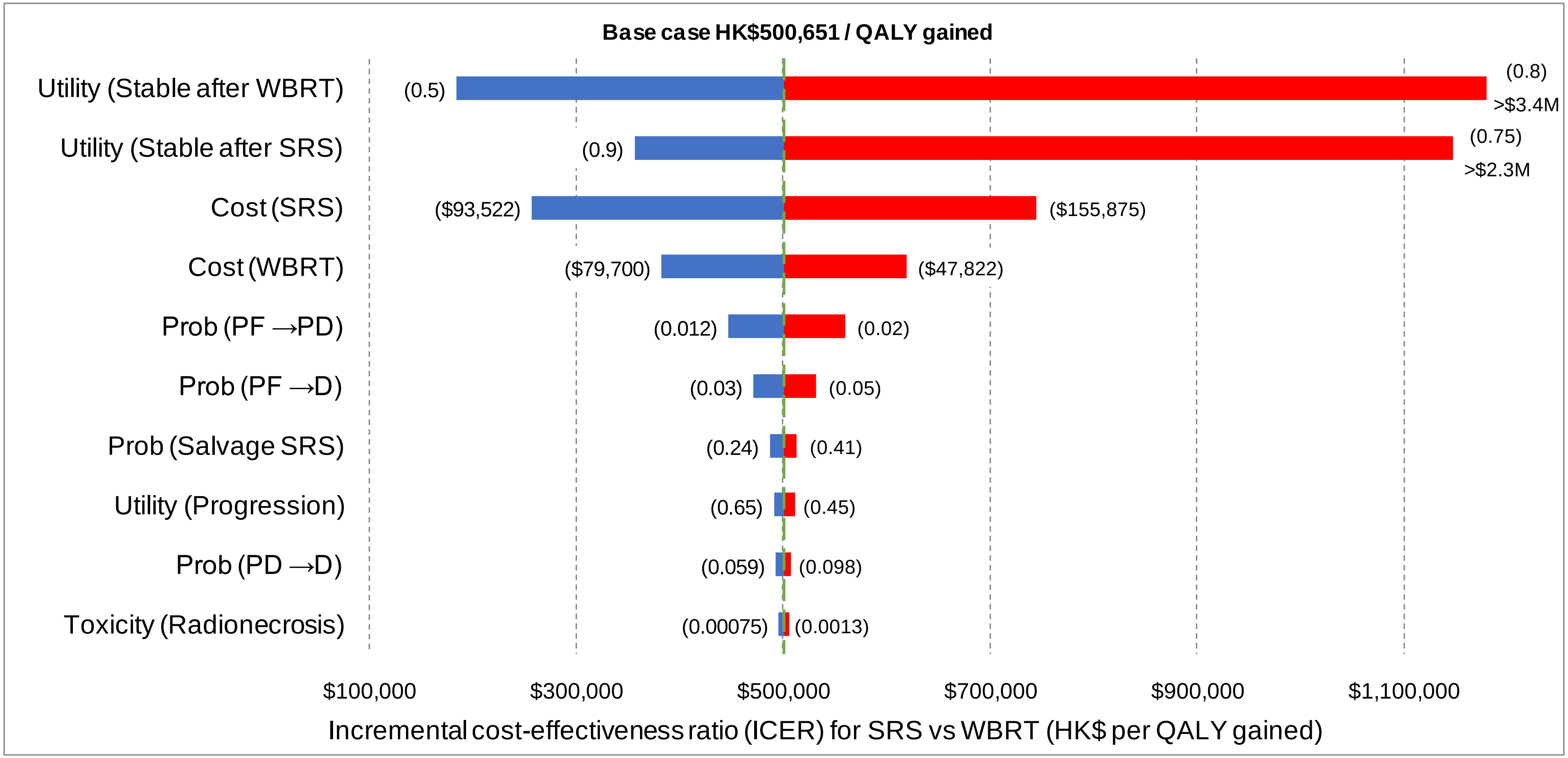
Results: base case

Base case	Cost (HK$) per individual	QALY per individual
WBRT only	$173,518	0.844
SRS only	$241,133	0.979

- Incremental cost-effectiveness ratio (ICER) = HK$500,651 / QALY gained (138% of GDP per capita)

One-way sensitivity analysis on ICER for SRS vs WBRT

$$\text{ICER} = \frac{\text{Incremental change in Cost}}{\text{Incremental change in Utility}} = \frac{\text{Cost (SRS)} - \text{Cost (WBRT)}}{\text{QALY (SRS)} - \text{QALY (WBRT)}}$$



Values in parentheses present the new values in sensitivity analysis, given other values remain unchanged.

ICER of SRS versus WBRT
Comparisons with other conditions (HK studies)

Condition	Year of study	Interventions	ICER per QALY (HKD)
1st line metastatic prostate cancer	2017	Abiraterone + hormone vs hormone alone	1,427,425
Metastatic malignant melanoma	2017	Check-point inhibitor vs chemo	414,359
Breast cancer (Her2+)	2015	Adjuvant 1-year Trastuzumab	484,318
Breast cancer screening	2015	Biennial MMG for women aged 40-69 years old	566,093
Organic acidemia	2016	Newborn screening	983,333
Influenza	2015	Quadrivalent influenza vaccine	813,407 (15-64 y.o.) 286,385 (65-79 y.o.) 62,907 (≥80 y.o.)
Brain metastases	2018	Stereotactic radiosurgery	500,651

SRS versus craniotomy for brain metastasis

- No head-to-head clinical trials comparing SRS and craniotomy

- Craniotomy for brain metastasis is indicated when
  - large brain metastasis causes mass effect / hydrocephalus / bleeding
  - histological proof of cancer diagnosis (when waiting time for craniotomy is even shorter than bronchoscopy for CA lung!)
  - waiting time of craniotomy (emergency OT) is even shorter than SRS

CEA studies: SRS versus craniotomy

Author	Year	Country	Interventions	Outcomes (HKD)
Rutigliano	1995	USA	SRS versus surgical resection	98,171 (ICER per QALY)
Vuong	2013	Germany	SRS versus surgical resection	35,026 (Insurance payment, SRS less costly)
Vuong	2013	Vietnam	SRS versus surgical resection	2,657 (patient's direct payment, SRS less costly)

- Surgical excision in general is more expensive than SRS due to operative cost and hospitalization cost.
- Surgical excision must also be followed by WBRT or SRS to lower the risk of surgical cavity recurrence (50% in 6 months). This markedly increases the overall cost

Discussion

- Cost-effectiveness of advanced RT technique (SRS alone) for brain metastases is similar, if not better, than other novel anti-cancer treatments in Hong Kong

- SRS is expensive and technically complicated. But uncontrolled brain metastases is also costly

- Cost of SRS can be further decreased by
    - Implementation of advanced planning technology and improve staff training
    - Changing the way we measure "performance indicators" by incorporating more weight in treatment planning and machine-time saving

Take home

- Brain metastases is common problem
- Poorly controlled brain metastases is difficult and costly to patients, families and the whole society
- Advanced RT has similar, if not better cost-effectiveness compared with other novel cancer treatments
- Newer technology, staff empowerment and updates of performance indicators will help to bring down the cost of advanced RT – and help more patients

Acknowledgements

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