HAIFU® MODEL- JC FOCUSED ULTRASOUND TUMOR THERAPEUTIC SYSTEM- AN UPDATE

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
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DISCLAIMER

Technology review is a brief report, prepared on an urgent basis, which draws on restricted reviews from analysis of pertinent literature, on expert opinion and / or regulatory status where appropriate. It has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

Please contact: htamalaysia@moh.gov.my, if you would like further information.

Health Technology Assessment Section (MaHTAS),
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya

Tel: 603 88831246

Fax: 603 88831230

Available at the following website: http://www.moh.gov.my

Author or authors:

Ku Nurhasni Ku Abd Rahim
Principal Assistant Director
Pharmacist
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by:
Datin Dr Rugayah Bakri
Public Health Physician
Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

External reviewer:
Dr. Gerard Lim Chin Chye
Senior Consultant (Oncology)
General Hospital Kuala Lumpur
Ministry of Health

Dr Mohd Rizal Roslan
Consultant Radiologist and Interventional Radiologist
Department of Radiology
Selayang Hospital
Ministry of Health

DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

High-intensity focused ultrasound which is also known as focused ultrasound ablation or focused ultrasound surgery is a hyperthermia therapy that uses temperature to treat disease. It uses ultrasound at high intensity and ultrasound beam is being focused at a specific target area to destroy cells. Typically, high-intensity focused ultrasound (HIFU) procedures are performed in conjunction with an imaging guidance namely magnetic resonance imaging (MRI) or diagnostic sonography as the imaging procedure enables the treatment planning and targeting before applying the ablative levels of ultrasound energy.

Malaysian Health Technology Assessment Section had produced a technology review report in 2011 on Haifu® Model JC, Model JC200 and Seapostar. However, this updated review included recent evidence on Haifu® Model JC as requested by the Director of Medical Practice Division, Ministry of Health.

Objective/aim

To assess the new evidence from 2011 onwards on the efficacy/effectiveness, safety and cost/cost effectiveness of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of solid tumor.

Results and conclusions

From the systematic search conducted in the available scientific databases and other websites, there was no retrievable systematic review or randomized controlled trial on Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of solid tumor. However, there were 8 literatures consisting of non-randomized single arm trials, case series, cohort study and case report on the efficacy/effectiveness and safety of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of patients with hepatocellular carcinoma, advanced pancreatic cancer and uterine fibroids which were included in this review. No recent evidence was retrieved on other types of solid tumor.

In conclusion, there were limited fair level of evidence from recent publications retrieved from the available scientific databases on the efficacy/effectiveness and safety of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for the treatment of hepatocellular carcinoma, advanced pancreatic cancer and uterine fibroid. Further research such as randomized controlled trial is warranted to provide high quality of evidence before it can be used as standard treatment for solid tumor.

Complications related to skin which were also reported in earlier technology review report were the most commonly reported complication from the available evidence. Other complications namely body temperature increase, abnormal cardiac rhythm, injuries of sternal vertebrae and vertebrae lumbales,

acute cholecystitis, nausea, ileus, anorexia and abdominal pain, transient pancreatitis,sacrococcyx pain, hip pain, radiating pain in the lower limbs, pancreatic fistula and gastrointestinal tract bleeding due to gastric ulcer have also been reported in the literature. Thus, it is important for the clinicians to monitor the adverse events during and after the HIFU treatment.

The cost-effectiveness of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of solid tumor cannot be determined as there were no local economic studies retrieved from the scientific databases.

Recommendation

Haifu ® Model-JC Focused Ultrasound Tumor Therapeutic System is recommended for research purpose to provide more high quality evidence.

Methods

Scientific electronic databases were searched through OVID interface which include MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews - Cochrane Central Register of Controlled Trials-December 2012. EBM Reviews – Database of Abstracts of Review of Effects (4th Quarter 2012), EBM Reviews - Cochrane database of systematic reviews - 2005 to November 2012 , EBM Reviews – Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment - 4th Quarter 2012 , NHS economic evaluation database - 4th Quarter 2012, Pubmed and USFDA website.

Last search was done on 16th January 2013 and there was no limitation during the search. Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US / Canadian Preventive Services Task Force

HAIFU® MODEL- JC FOCUSED ULTRASOUND TUMOR THERAPEUTIC SYSTEM- AN UPDATE

1. INTRODUCTION

Ultrasound technology in clinical practice is no longer limited to diagnostic purposes only. Over the past two decades, there have been dramatic developments in medical imaging techniques which have driven the evolution towards greater use of non–invasive therapy such as high-intensity focused ultrasound as a potential therapy for solid tumors.[1,2]

High-intensity focused ultrasound which is also known as focused ultrasound ablation or focused ultrasound surgery is a hyperthermia therapy that uses temperature to treat disease. It uses ultrasound at high intensity and ultrasound beam is being focused at a specific target area to destroy cells.[3] Typically, high-intensity focused ultrasound (HIFU) procedures are performed in conjunction with an imaging guidance namely magnetic resonance imaging (MRI) or diagnostic sonography as the imaging procedure enables the treatment planning and targeting before applying the ablative levels of ultrasound energy.[4]

Malaysian Health Technology Assessment Section had produced a technology review report in 2011 on Haifu® Model JC, Model JC200 and Seapostar. However, this updated review included recent evidence on Haifu® Model JC as requested by the Director of Medical Practice Division, Ministry of Health.

2. OBJECTIVE/AIM

To assess the current evidence from 2011 onwards on the efficacy/effectiveness, safety and cost/cost effectiveness of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of solid tumor.

3. TECHNICAL FEATURES

The Chongqing Haifu was founded in the year of 1999 and was developed by Chongqing Haifu (HIFU) Technology Co.,Ltd. The Haifu System uses a patented transducer with powerful, cutting-edge ultrasound technology that delivered treatment from outside the body, leaving no scar with minimal pain.[5]

It enables the treatment of solid tumors using principles of surgical oncology. The 3-D conformal technology allows ablation of both malignant and benign tumors. Malignant tumors are targeted to include specific volume of normal surrounding tissue while benign tumors may be treated up to their margin. A planning session is performed to identify the target tumor volume. Subsequently, it is divided into parallel slices and the entire volume of the target tumor can be treated slice by slice based on the position and depth of the target.[3,5] The onboard software

package allows the clinicians to have a visual and capture images of the target tumor before integrating them with the therapy control system.[3]

The table below illustrate the technical specification of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System.[4,5]

Table 1: Technical Specification of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System

PARAMETER	SPECIFICATIONS
Electric Power	Power input:12.5 kVA
Operating frequency	0.8 MHz
Acoustic output	Acoustic power: 0-400 W, adjustable
Focal field	i. Acoustic intensity 5000 W/cm2-20000W/cm2 ii. Shape of focal field: Ellipsoidal in milimeter
Focal length of treatment head	90-169 mm
Coupling water	i Oxygen content in coupling water: 5 ppm ii. Water level: 0-800 mm, continuously adjustable iii. Water temperature: 5-40 ºC iv. Water flow: 0-10 l/min, adjustable
Movement	i. Lineal movement range of motional devices: X = 120 mm, Y = 120 mm, Z = 120 mm ii. Rotary angle of Gamma motion device: ≥ 60º iii. Rotary angle of Chi motion device: ≥ 20º iv. Rotary angle of Theta motion device: ≥ 180º v. Horizontal movement range of treatment bed: 130 mm vi. Vertical movement range of treatment bed: 250 mm
Installation Environment	Installation area ≥ 40 m2 Height ≥ 2.8 m Width ≥ 5.8 m Load per m2 after installation 1400 kg/m2 Tap water pressure ≥ 0.2 MPa Supplied water temperature ≤ 30ºC Power input: 12.5 kVA Operation Room: 20-30 ºC

Figure 1: Haifu® Model-JC Focused Ultrasound Tumor Therapeutic

Among the indications of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System that have been listed by the manufacturer are pancreatic cancer, uterine fobroids, multiple myoloma, bone tumor, breast cancer and liver cancer. Furthermore there are clinical advantages claimed by the manufacturer namely:

- Preserve organ and structure
- No incision ,no radiation damage
- Conformal treatment
- Activate immune system
- One time treatment
- Safe and effective treatment
- Shorter hospitalization time
- Green Technology

4. METHODS

4.1. Searching

Electronic databases searched through the Ovid interface;

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present
- EBM Reviews - Cochrane Central Register of Controlled Trials-December 2012
- EBM Reviews – Database of Abstracts of Review of Effects (4th Quarter 2012)
- EBM Reviews - Cochrane database of systematic reviews - 2005 to November 2012
- EBM Reviews – Cochrane Methodology Register 3rd Quarter 2012
- EBM Reviews - Health Technology Assessment - 4th Quarter 2012
- NHS economic evaluation database - 4th Quarter 2012

Other databases:

- PubMed
- USFDA website

Literature search was done from year 2011 to current as the previous technology review report in 2011 has included the article from early 2011 and below. Last search was done on 16th January 2013 and there was no limitation during the search. Google was used to search for additional web-based materials and information. Appendix 1 showed the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Solid tumors
Interventions	Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System
Comparators	-
Outcomes	Survival “Reduction of tumor size” Disease progression
Study design	• Systematic Review, Randomized Controlled Trial, Observational studies which were not included in MaHTAS Technology Review Report (Serial num:022/2011) • Articles retrieved from literature search (from year 2011 to current) • Articles contributed through personal

	communication with the industry (from year 2011 to current)
	English full text article

Exclusion criteria

Study design	• Animal studies, Editorial Letter and Narrative Review • Articles included in MaHTAS Technology Review Report (Serial num: 022/2011)
	Non English full text article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix

5. RESULTS AND DISCUSSION

From the systematic search conducted in the available scientific databases and other websites, there was no retrievable systematic review or randomized controlled trial on Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of solid tumor. However, there were 8 literatures consisting of non-randomized single arm trials, case series, cohort study and case report on the efficacy/effectiveness and safety of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of patients with hepatocellular carcinoma, advanced pancreatic cancer and uterine fibroids which were included in this review. No recent evidence was retrieved on other types of solid tumor.

It was found that high intensity focused ultrasound (HIFU) treatment was performed under general anesthesia in hepatocellular carcinoma and advanced pancreatic cancer patients. Meanwhile, treatment was performed under conscious sedation in uterine fibroids patients.

5.1. EFFICACY/EFFECTIVENESS

5.1.1 Hepatocellular carcinoma

Ng KC et al conducted a study on 49 unresectable HCC who received HIFU treatment and reported that 1 and 3 year overall survival rates were 87.7% and 62.4% respectively and the 1 and 3 year disease-free survival rates were 40.7% and 0% respectively. The authors also reported that the primary technique

effectiveness rate which defined as the percentage of tumors that were successfully eradicated following initial course of HIFU was 79.5% (39 out of 49 patients) while 10 patients (20.4%) had residual tumors 1 month after treatment with 3 of them were rendered-tumor free after radiofrequency ablation. Hence, the overall effectiveness rate was 85.7% (42 out of 49 patients). Meanwhile, the overall recurrence rate was 61.9% (26 of 42 patients) with 9 of the patients (21.4%) developed local recurrence while others developed intrahepatic tumor recurrence. [7] Level II-2

Although lipiodol has been suggested to reduce tumor blood supply and increase the deposition of the ultrasonic energy in the tumor, the findings revealed that there was no statistically significant difference in the percentage of tumors that were successfully eradicated following the initial course of HIFU between patients that was treated with HIFU alone than those with HIFU and pretreatment of transarterial injection of iodized poppyseed oil (Lipiodol) deposition. [7] Level II-2

The authors also suggested that the only significant possible prognostic factors affecting the overall survival after HIFU was Child-Pugh liver function. In addition, they suggested that tumor size ≥ 3 cm was a significant risk factor for incomplete ablation in patients with hepatocellular carcinoma based on the explanation that large tumors require longer ablation time by the HIFU resulting in cutaneous and subcutaneous tissue edema that will reduce the targeting ability of the diagnostic ultrasound of the HIFU machine. [7] Level II-2

Xu G et al conducted a study in 145 patients with primary hepatocellular carcinoma (HCC), (15 stage II, 25 stage IIIA. 42 stage IIIB, 40 stage IIIC and 23 stage IV) and found that survival appeared significantly better in patients with low stage HCC where HIFU could target the whole tumor area ($p<0.05$). The authors also found in their observation that 34 patients (23.4%) had total tumor necrosis while 43 patients (29.7%), 29 patients (20%) and 39 patients (26.9%) had a necrosis area > 75%, >50% and less than 50% respectively. In addition, the post HIFU serum α-fetoprotein (AFP) levels decreased significantly with the total decrease rate of 71.7% for 106 patients who had high AFP levels before the HIFU treatment. [8] Level II-3

In view of the short-term efficacy in hepatocellular carcinoma patients, abdominal pain relief was the most evident of symptom relief with 84.8% followed by appetite loss, jaundice and bloating ranged from (76.3%-37.5%). [8] Level II-3

A case report of hepatocellular carcinoma patient awaiting liver transplantation was produced by Cheung TT et al and found that the magnetic resonance imaging performed after one month of the HIFU treatment revealed complete ablation of the tumor lesion. No complication was reported after the operation.[9] Level III

5.1.2 Pancreatic Cancer

A study of 40 advanced pancreatic cancer patients (stage III and IV) by Wang K et al showed that the median overall survival time was 10 months and 6 months for patients with stage III and IV disease respectively. The median overall survival (OS) time, 6 months and 1 year-survival rate for patients as a whole were 8 months (95% CI, 4.5 to 11.5), 58.8% and 30.1% respectively. In addition, the author found that the median local progression free survival (PFS) time for all patients was 5 months (95%CI, 4.6 to 5.4).[10 Level II-2]

The authors also reported that 7 advanced pancreatic cancer patients achieved partial response which is equal to 17.5% overall response rate. The author defined partial response as a 50% reduction in the maximum perpendicular tumor measurements for at least 1 month. Meanwhile, 28 patients (70%) had no change and 5 patients (12.5%) had a progressive disease. [10 Level II-2]

Similar observation by Sung Y et al which involved 46 advanced pancreatic cancer patients revealed that in most of the advanced pancreatic cancer patients, the HIFU ablated lesions remained unchanged, without any progression. However, it has been suggested that extrapancreatic metastases might have occurred. In addition, it was found that overall the survival rates at 6, 12 and 18 months from HIFU therapy were 52.2%, 30.4% and 21.79% respectively.[11 Level II-2]

There was a significant difference ($p<0.001$) in the average degree of pain compared with pre-HIFU pain score as observed by Sung et al in advanced pancreatic cancer patients at one month after the procedure while findings by Wang K et al showed that 52.2% - 65% patients experienced a partial relief of pain respectively. Moreover, 22.5% received entire pain relief. [10,11 Level II-2]

5.1.3 Uterine Fibroids

Wang W et al reported that enlargement of residual fibroid was seen in 4 out of 76 submucosal uterine fibroid patients, who then had received additional HIFU ablations. The authors also revealed long term efficacy of HIFU treatment as the ablated fibroids shrank significantly over time with the average volume shrinkage at 3,6,12 and 24 months was 46.7%, 68.2%, 78.9% and 90.1% respectively. It was also reported that the volume of menstrual bleeding decreased significantly ($p<0.05$) in 55.3%, 71.1% and 89.5% of sub mucosal uterine fibroid patients at the first menstrual period, 3 and 6 months after HIFU ablation respectively [12 Level II-2]

Uterine fibroids used to be classified based on T2- weighted MRI as hypointense, isointense and hyperintense. As reported by Zhou WP et al, non-perfused volume (NPV) ratio of hypointense, isointense and hyperintense fibroid after HIFU treatment was 86.3±11.9%, 77.1±16.5% and 67.6±23.9%. The NPV

indicates successful ablation. The author also reported that there were three slightly homogeneous hyperintense fibroids with no NPV after HIFU treatment.[13] Level II-3

5.2. SAFETY

The manufacturer claimed that Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System have received ISO 9001, ISO 13845 and CE certificate and various international patent and approval such as from South Korea, Russia, Japan, Canada, United States, Australia and Singapore.

Xu G et al showed that one major complication during HIFU therapy was the local skin burn with 37.2% experienced Grade 1, 31.7% Grade 2 and 2.1% Grade 3. The authors also suggested that skin burn is caused by the accumulated heat in the skin during HIFU treatment which is associated with the ultrasound intensity and treatment time [8] Level II-3

Similarly, skin related complication has also been reported in various studies with Ng KC et al suggested that the complication was due to an error of using high acoustic power. [7,10,11] Level II-2, [13] Level II-3

In contrast, Wang K et al reported that there was no evidence of skin burn, as well as haematological toxicity and bleeding or infection overlaying the treated lesion.[9] Level II-2

There were also other complications that have been reported during the HIFU treatment which include body temperature increase, abnormal cardiac rhythm, injuries of sternal vertebrae and vertebrae lumbales, acute cholecystitis, nausea, ileus, anorexia and abdominal pain, transient pancreatitis, sacrococcyx pain, hip pain, radiating pain in the lower limbs, pancreatic fistula and gastrointestinal tract bleeding due to gastric ulcer. However, transient local pain and elevated pancreatic enzyme were subsided within few days.[8] Level II-3 , [11] Level II-2, [13] Level II-3

It was reported that the HIFU treatment time varied with different type of cancer ranged from 3 to 250 minutes.[7,10-12] Level II-2, [8,13] Level II-3, [9] Level III It was also suggested that treatment time is a potentially important issue for clinical application according to the volume of the tumor.[13] Level II-3 Meanwhile, other literature suggested that the HIFU device which employing a higher intensity has a higher incidence of adverse events.[14]

5.2.1 Hepatocellular carcinoma

Ng KC et al reported that one hepatocellular carcinoma patient had chest wall bruising caused by bleeding from intercostals vessels that were injured during induction of artificial pleural effusion in patients with tumors near to the diaphragm. [7] Level II-2

5.2.2 Pancreatic cancer

During the hospital stay, there were no signs of tumor haemorrhage, large blood vessel rupture obstructive jaundice or gastrointestinal perforation. There were also no severe complications or adverse events related to HIFU treatment reported during the follow up period.[10 Level II-2]

5.2.3 Uterine fibroids

For uterine fibroids patients, none has developed amenorrhea that may be caused by irreversible thermal damage to the endometrium after HIFU ablation. There were also no other major complications such as bowel perforation and nerve damage that has been observed.[12 Level II-2]

In another study by Qin J et al involving 435 women, unplanned pregnancy was reported by 24 women within 1 year of treatment. Out of 24 women, eight of these women had desired pregnancy before undergoing the treatment while others had not intended to become pregnant before HIFU treatment. Seven women, who had desired pregnancy before undergoing HIFU treatment continued pregnancy without any complications, while other 17 women underwent either induced or spontaneous abortion.[15 Level III]

5.3 COST/COST-EFFECTIVENESS

There was no retrievable scientific evidence addressing the cost-effectiveness of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of solid tumor particularly local economic studies

5.4 LIMITATIONS

- Selection of studies was done by one reviewer and reviewed by another reviewer.
- Although there was no restriction in language during the search but only English full text articles were included in this report.
- Articles retrieved may include articles from previous years as it is being indexed in the selected year of database.

6. CONCLUSION

In conclusion, there were limited fair level of evidence from recent publications that were retrieved from the scientific databases on the efficacy/effectiveness and safety of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System

for the treatment of hepatocellular carcinoma, advanced pancreatic cancer and uterine fibroids. Further research such as randomized controlled trial is warranted to provide high quality of evidence before it can be use as standard treatment for solid tumor.

Complications related to skin which were also reported in earlier technology review report were the most commonly reported complication from the available evidence. Other complications namely body temperature increase, abnormal cardiac rhythm, injuries of sternal vertebrae and vertebrae lumbales, acute cholecystitis, nausea, ileus, anorexia and abdominal pain, transient pancreatitis, sacrococcyx pain, hip pain, radiating pain in the lower limbs, pancreatic fistula and gastrointestinal tract bleeding due to gastric ulcer have also been reported in the literature. Thus, it is important for the clinicians to monitor the adverse events during and after the HIFU treatment.

The cost-effectiveness of Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System for treatment of solid tumor cannot be determined as there were no local economic studies retrieved from the scientific databases.

7. REFERENCES

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8. APPENDIX

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1. exp Neoplasms/
2. tumor*.tw.
3. neoplas*.tw.
4. ((benign or malignant) adj1 (neoplas* or tumo?r*)).tw.
5. (solid adj1 (tumo?r* or malignanc*)).tw.
6. exp High-Intensity Focused Ultrasound Ablation/ or exp Ultrasonic Therapy/ or exp Ultrasonics/ or high intensity focused ultrasound.mp.
7. (ultrasonic adj1 therap*).tw.
8. focal ablation treatment.tw.
9. focal therapy.tw.
10. ultrasonography.tw.
11. focused ultrasound therapy.tw.
12. high intensity focused ultrasound therapy.tw.
13. ablation.tw.
14. exp Survival/ or exp Survival Rate/ or exp Disease-Free Survival/
15. (survival* adj1 (rate* or time* mean or disease-free or event-free or progression free)).tw.
16. (mean survival* adj1 time*).tw.
17. "reduction tumor size".mp.
18. "decrease alfa-fetoprotein levels".mp.
19. 1 or 2 or 3 or 4 or 5
20. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
21. 14 or 15 or 16 or 17 or 18
22. 19 and 20 and 21

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Database of Abstracts of Review of Effects	
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	
USFDA	Haifu® Model-JC Focused Ultrasound Tumor Therapeutic System

8.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)