Assessment of Modern Radiotherapy Techniques for Breast Cancer Treatment in Indonesia

Nur Rahmah Hidayati, Nastiti Rahajeng and Prasetya Widodo
Center for Technology of Radiation Safety and Metrology, National Nuclear Energy Agency, Jl. Lebak bulus Raya No. 49 Kotak Pos 7043 JKSKL, Jakarta Selatan 12070, INDONESIA
E-mail: inn98@batan.go.id

Abstract. **Breast cancer has been delineated as women's cancer due to the increasing of the incidence of this cancer in women around the world. In Indonesia, breast cancer has placed as the first rank with 36.2/100,000 incidents. Another data from GLOBOCAN 2008 reported that the estimated incidence for breast cancer in Indonesia is 25.5% of total cancer incidence, with mortality rate 19.2 % of total cancer mortality. Since breast cancers can be cured in early stage, an establishment of cancer management should be done by promoting radiotherapy as one of treatment options. It is important to assess the modern radiation therapy techniques which can improve treatment outcomes in breast cancer management, especially in developing countries, such as Indonesia. The main objective of this article, is to assess modern radiotherapy techniques which are clinically used for breast cancer treatment, and to assess the possibility of the technique to be applied as an option for treating the breast cancer in Indonesia. The assessment method has been done by literature study and found that there are few options in modern radiotherapy such as brachytherapy, external beam radiation therapy and charged particle therapy. However, Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Radiation Therapy (VMAT), as a form of external beam radiation therapy can be used as the best option of favorable techniques for breast radiotherapy in Indonesia due to it's abillity to reduce the radiation dose delivered to the organs at risk. In addition, brachytherapy might become an option in the future.**

Keywords: breast cancer, radiotherapy, modern radiotherapy modalities

Introduction

The world's statistic of cancer in women has shown that breast cancer is the most common incidence in women. As a consequence, breast cancer has been delineated as women's cancer (Ludwig H, 1994). In Indonesia, breast cancer has placed as the first rank with 36.2/ 100000 incidents (Georgakilas, 2012). Another data from GLOBOCAN 2008 reported that the estimated incidence for breast cancer in Indonesia is 25.5% of total cancer incidence, with mortality rate 19.2 % of total cancer mortality (Ferlay et al, 2010). For this reason, the awareness about the fighting to breast cancer should be established by promoting early stage diagnosis, and followed by the right option in cancer management (Kimman M, 2012).

A cancer management is commenced when a patient has been diagnosed having cancer and continued by treatments, such as palliative surgery, radiation therapy and chemotherapy (WHO, 2012). However, from the available treatment methods, radiation therapy (radiotherapy) has been acknowledged as a significant method to kill cancer cell solely, and /or together with hormone therapy or chemotherapy or surgery (Barton, et al., 2006)0. Radiation therapy or radiotherapy has been defined as a medical therapy using radiation beams to kill cancer cells in human body. In breast cancer cases, radiotherapy could be given as adjuvant therapy following mastectomy, definitive therapy following surgery and palliative therapy on metastatic locations (Williams and Thwaites, 1993).

In order to kill cancer cell in human body, there are different kinds of treatment radiotherapy methods which can be used to deliver radiation energy into human body, namely, radionuclide therapy, brachytherapy, external beam radiation therapy (EBRT) and particle therapy (Metcalfe et al. 2007). However, the most established radionuclide therapies are treatment for thyroid gland cancers, hematologic cancers and bone metastases (Brans et al., 2006). Hence EBRT, brachytherapy and particle therapy are the primary concerns.

This article is intended to assess modern radiotherapy techniques which are clinically used for breast cancer treatment in the world, and find the possibility of the technique to be applied as an option for treating breast cancer in Indonesia.

Conventional Radiotherapy

In conventional radiotherapy, external beam radiotherapy refers to utilization of high energy X-ray or electron beam from a basic linear accelerator or a cobalt-60 beam (Mayles et al., 2007). A pair of beams in the opposed tangential directions is delivered to kill cancer cells in a particular energy range. Since the energy range typically is between 100 kV to 25 MV, it has led to the biological damage of normal tissue adjacent the cancer (IAEA, 2008).

A significant feature from conventional radiotherapy is the application of 2D X-ray films to support the treatment delivery decision. This feature makes it really different from modern radiotherapy, since modern radiotherapy utilize an output from modern imaging devices such as computed tomography X-ray (CT scan), magnetic resonance imaging, and electronic portal imaging device (EPID) (Thariat et al. 2012). In addition, the transformation from conventional to modern radiotherapy also has been integrated by the development of computer hardware and software (Khan, 2010).

Modern Radiotherapy

Modern radiotherapy makes it possible to create a normal dose distribution of radiation beam during the delivery of radiation dose to the patients (Fraass and Moran, 2012). It ensures that the radiation beams can kill cancer cells, while the normal t issues adjacent the target organs receive a number of radiation doses as low as possible (Levitt et al., 2012). The development of imaging technology has promoted the manufacturers in medical linear accelerators to produce advanced radiation treatment delivery methods. It makes the optimization of radiation patterns in Three Dimensional Conformal Radiation Therapy (3DCRT) give a maximum dose to the target and a minimum dose to surrounding organs (Metcalfe et al. 2007)0. Moreover, each beam might be assigned by using a three-dimensional computer radiotherapy treatment planning (3DRTP) software to produce a 2D dose display (Khan, 2010)0. With the assistance of dose display, a computation of 3D dose to PTV can be evaluated by considering the tumor control probability (TCP) and normal tissue complication probability (NTCP). As a result, these planning data are sent to the machine after a verification of patient position, beam placement and dosimetry aspects (IAEA, 2008).

Volume definition in radiotherapy

When a patient has been referred to be treated with radiation therapy, a radiation oncologist will prescribe the treatment dose and consider some volume of tissue adjacent the tumor site. For these purposes, some terms in delineation of the tumor (target organ) and normal tissue have been introduced by the International Commission on Radiation Unit and Measurements (ICRU) in reports 50, where the terms for specific volume targets namely are: the gross tumor volume (GTV), planning target volume

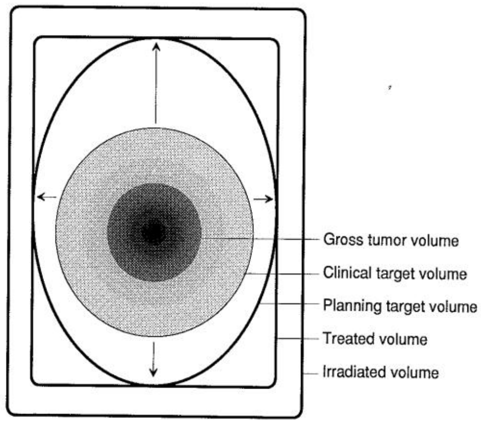

Figure 1. Definition of target volumes as stated in ICRU Report, reprinted from ICRU Report no.50 and 83, respectively (IAEA, 2008).

(PTV), clinical target volume (CTV), target volume and irradiated volume (see Figure 1) (ICRU, 1993).

Recently, the ICRU Report has been updated with the report number 83, which presented new terms in volume definitions, namely organ at risk (OAR), planning organ at risk volume (PRV), internal target volume (ITV), treated volume (TV), remaining volume at risk (RVR) ((ICRU, 2010). The new terms refers to the consideration of delivered dose in by setting up an internal margin for the organ target. For example, an internal margin for breast cancer radiation therapy will consider the variation of the shape, size and position of the tumor with regard to the surrounding organs' such as heart, lungs, muscles, and ribs (Hoskin P, 2012).

A qualitative assessment of treatment planning can be done by evaluating the cumulative dose volume histogram (DVH) which displays the volume (or percentage of total organ volume) that receives at least a certain dose threshold (see Figure 2) from reference (Allen et al. 2012). Figure 2.a denotes the DVH for an ideal situation, while Figure 2.b represents the DVH in practice. However, an ideal DVH is difficult to be achieved, since the PTV practically receives less than 100% of the prescribed dose as a result of the PTV overlaps with surrounding organs (Allen et al. 2012).

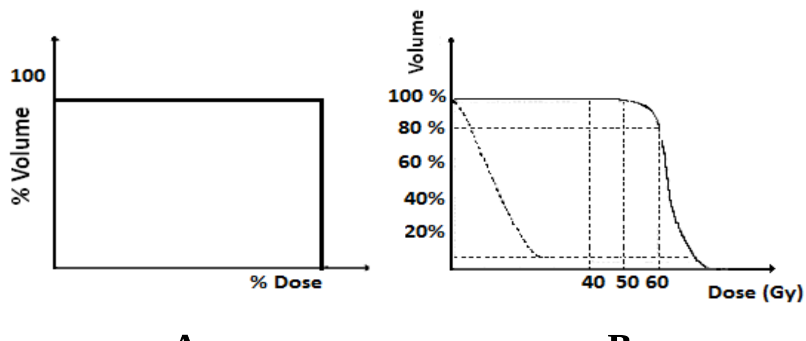

Figure 2. A comparison between an ideal DVH (A) and a practice's DVH (B) (Allen et al., 2012). (Reprint from CSIRO Publication: Biomedical Physics in Radiotherapy for Cancer, permission requested).

Intensity Modulated Radiation Therapy (IMRT)

The utilization of modern multi leaf collimator (MLC) was started in 1980 to replace the conventional collimator. The modern MLC consists of 80 pairs of leaves that have capability to shape modulated beams (Khan, 2010)0. As a result, an advanced method of 3DCRT, called as intensity modulated radiation therapy (Purdy, 2001), has been investigated. Since MLC creates the shaped beams driven by computerized system, it allows the beams move automatically during the beam delivery process. Moreover, the radiation contours can be fitted more closely around the target organ to give a true conformal dose distribution of the PTV. Consequently, for a given radiation dose, the harmful effect to the adjacent organs will be lower (Purdy, 2001; Rudat et al., 2011).

Figure 3 shows a comparison of beam delivery of the IMRT and the 3DCRT. It illustrates that the IMRT has capability to create the dose distribution with a concave shape, despite the time needed to do an iterative optimization might be longer than that of the 3DCRT (ICRU, 1993). This advantage makes the IMRT chosen as the new treatment modality, replacing the 3DCRT to kill localized cancers (Ahamad et al., 2005). Furthermore, a review of clinical applications has shown that the IMRT can reduce toxicity in radiotherapy treatments for breast cancer (Bhide and Nutting, 2010).

Image-Guided Radiation Therapy

With the advantage of high quality of CT or MRI images during treatment planning process, IMRT has achieved better modulated beam to the target organs (Ling et al., 2006). However, during the treatments, there are some important factors which affect the precision of dose delivery, such as interfraction motion within cancer sites, patient motion during the treatment and the deformation of tumor shapes (Herk, 2007). Those factors can play as a source of error such as misalignment and overdose. Hence, in order to control the motion as a source of error, an advanced IMRT has been initiated as the image-guided radiation therapy by utilizing ionizing imaging devices during the treatment process, such as X-ray, and CT scan, as well as non ionizing radiation

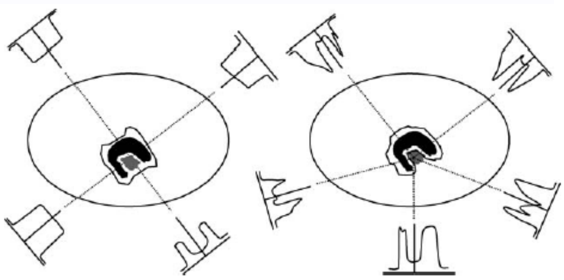

Figure 3. Comparison of beam delivery in 3DCRT (left) and IMRT (right), reprinted from ICRU Report no.83, reference (ICRU, 1993).

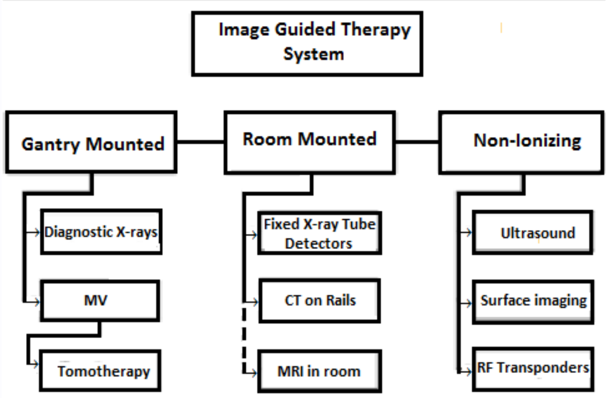

Fig 4. A schematic of combined imaging system in IGRT, the dashed line is shown as the system under development. The horizontal connecting lines indicate possible combinations with different hardware configurations, reprinted from reference (Chen et a l., 2009)0 (permission requested from Springer: Radiological Physics and Technology).

imaging devices such as ultrasound and MRI (see Figure 4) (Chen et al., 2009).

Volumetric Modulated Radiation Therapy (VMAT)

Following the development in radiation therapy methods, Linac vendors have released machines which are able to change the dose rate variation and the speed of gantry. This development leads to the increasing treatment sites that can be treated using external beam radiation therapy, especially in some complicated sites where IMRT cannot be performed effectively (Matuszak, 2010). In 1995, from the reference (in Otto, 2008), Cedric Yu developed Intensity Modulated Arc Therapy (IMAT) to achieve the improvement of flexibility in high conformal radiation. Furthermore, a development called Volumetric Modulated Arc Therapy has overcome some IMAT's limitation by delivering beam in single gantry arcs in 360 degree range of gantry while includes dose rate and gantry speed variation. As a result, the radiation dose is lower, the delivery is shorter, and the total body scatter dose is lower (Walton and Broadbent, 2008). Hence VMAT is a method with combination of effective, flexible and optimized radiation therapy (Ruther, 2000).

Brachytherapy

Brachytherapy technique employs sealed radioactive sources to be placed into adjacent cancer sites. Basically, brachytherapy is not a modern radiotherapy technique since it has been used for more than 100 years (Nicolini et al., 2009). A categorization based on the delivered dose has been acknowledged, namely low dose (LDR) , with a dose rate of less than 2 Gy per hour, high dose rate (HDR), with a dose rate of between 2 and 12 Gy per hour and a medium dose rate (MDR) for the dose between LDR and HDR (Inoue, 2009).

The application of treatment planning software and the modern afterloading system makes the insertion of radioactive become the important technique in modern radiotherapy (Saphiro, 2002), since the digital imaging devices has significant role in defining the accuracy of the insertion of radioactive sources to be placed adjacent the target (Robinson, 2008). There are several radioisotopes which can be used as barchytherapy sources, but only few isotopes are commonly used, such as Co-60, Cs-137, Au-198, Ir-192, I-125, and Pd-103. A summary of physical characteristic of some brachytherapy sources has been listed in Table 1. Hoskin and Coyle (2001) provides the physical characteristic data of common brachytherapy sources. All sources are man-made radiation sources which have been produced using neutron activation in nuclear research reactor.

Brachytherapy can be performed by using an interstitial or intracavitary insertion method, depending on the location tumor sites (Podgorsak and Kainz, 2006). In breast cancer treatment, HDR interstitial brachytherapy may be used temporarily in the location adjacent the cancer (Polgar and Major, 2009) and it could be given after breast conserving surgery (Rulli et al., 2010). A recent technique called as accelerated partial breast irradiation (APBI) has been applied using brachytherapy technique (Lettmaier et al., 2011). Furthermore, a recent study shows that brachytherapy in APBI give less toxicity to adjacent organs and reduced treatment time (Gomeziturriaga, 2008).

Particle therapy

The principle of particle therapy is similar to EBRT. In EBRT, photon is used as the radiation beams, while in particle therapy, the radiation beams are originated from charged particles such as, proton, neutron or light ion therapy (Spoelstra and Senan, 2008). However, at the moment only protons and carbon ions are clinically used, because particle therapy, especially proton therapy, has highly conformal and homogenous radiation beam (MacDonald et al., 2006). These unique characteristics of proton beams are caused by protons depositing their energy until a particular range, called as Bragg peaks, depending on the energy. As shown in Figure 6, a variation of the intensity and the energy of the particles, the modulated Bragg peak can be arranged from the energy of beams. As it is shown, the Bragg peak of protons has been achieved at a depth of ± 150 mm, with the smaller dose is delivered compared to the EBRT beams (10 MV photons) (Levin et al., 2005)0.

Table 1. Physical characteristic of brachytherapy sources.

Isotope	Form	Half life	Average photon energy (MeV)
Co-60	Pellet	5.26 years	1.25
Cs-137	needles, tubes, pellet	30 years	0.66
Au-198	Seeds	2.7 days	0.41
Ir-192	Wire	73.8 days	0.38
I-125	Seeds	60 days	0.028
Pd-103	Seeds	days	0.021

The significant features of proton therapy have been acknowledged to give some disadvantages to pediatric patients. Despite that their critical organs can be avoided to receive the unintended radiation doses, pediatric patients have smaller size body, where some critical organs are really close each others. Moreover, they are still young and their organs are more sensitive to radiation beam (Dinesh Mayani, 2001). On the other hands, since proton therapy also creates internal radiation due to neutron interaction as a result of scattering protons, it can lead to the induction of secondary cancer risk due to low doses to the rest of body. It means that proton therapy may have a higher risk of secondary cancer, more than photon therapy (EBRT) for pediatric patients (Yoon et al., 2010).

In breast cancer, proton therapy has been projected to reduce the dose to heart and lung (Björk-Eriksson and Glimelius, 2005; Dowdell et al., 2008) as it has been reported in a comparative study using Intensity Modulated Proton Therapy (IMPT) and IMRT. Proton therapy is able to give lower dose to organ at risks (OAR) (Weber et al., 2004); Macready, 2012). However, since the operational cost of proton therapy is relatively high, the proton therapy is unlikely to be cost-effective (Anonimous, 2012) radiation therapy (Zelefsky et al. (2012), and needs an analysis of socio-economic cost effective before it has been used as a standard therapy (Spoelstra and Senan, 2008).

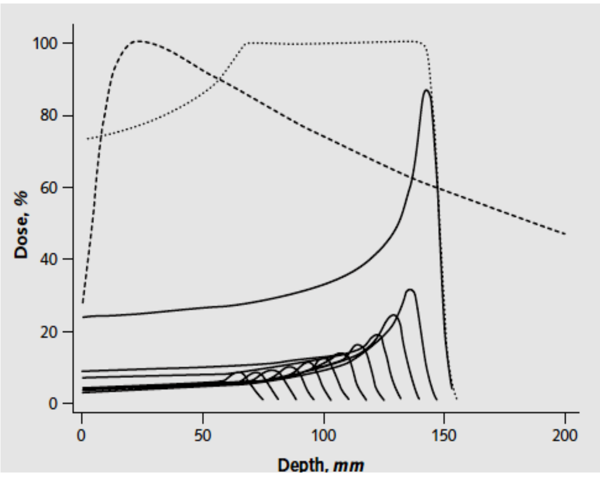

Figure 5. Dose distribution of a spread out Bragg peak of a particle beam compared 10 MV photon beams (Levin, 2005) (adapted with permission from Nature Publishing Group : *British Journal of Cancer*).

Discussion

The main findings show that the updating techniques in modern radiotherapy have attempted to achieve better sparing dose to normal tissues in order to kill cancerous tissue effectively. In order to find the best technique to spare healthy tissue, the references in proton therapy show that proton therapy gives better dose distribution compared to any other radiation therapy techniques and give benefits for breast cancer treatment. In addition, the updating technique such as IMPT also contributes better modulated proton beams in radiotherapy treatment. Unfortunately, most proton therapy facilities are built in high income countries such as US, China, Japan, etc (MacDonald et al., 2006)0.

Furthermore, a recent concern about secondary cancer due to modern radiation therapy has come up during the study (Ruther et al., 2000; Nicolini et al., 2009). Despite that the normal health tissue has been maintained to receive as low as possible dose, but it cannot avoid the probability of secondary cancer due to receiving low radiation dose during radiation treatment. However, a counter argument stated that nevertheless radiotherapy has secondary cancer risk, but the risk can be outweighed by the extension of life expectancy in cancer patients after radiation therapy (Zelefsky et al., 2012).

In addition, it is clear that the beam machines, imaging devices and the treatment planning software are the three important devices in development of modern radiotherapy, but beam machines are the most expensive equipment and play important role in the establishment process of breast cancer management. Furthermore, the more developed technology, the more expensive operation and treatment cost will be. Hence, not all modern radiotherapy can be applied for breast cancer management in low and middle income country like Indonesia.

Due to the lack of academic publication in application of radiotherapy techniques in Indonesia, it is hard to find the current data regarding application of radiotherapy in breast cancer management in Indonesia. As a result a popular article has been found that a hospital (Anonimous, 2012a) has utilized Rapid Arc, a trademark of VMAT from Varian (Anonimous, 2012b), and IMRT (Zelefsky et al., 2012) as standard in radiotherapy. It means that there is possibility to use advanced radiotherapy technology in breast cancer management in Indonesia, and there are a lot of chances to develop the technique not only for breast cancer but also for any other cancer sites. Moreover, these techniques are better and advanced in radiotherapy, but the publication of both methods is still far from number in Indoneisa academic journal. Hence, it needs to be published more in order to share the knowledge and increase public information about the availability of modern radiotherapy in Indonesia.

On the other hand, since the hospital has already utilized IMRT as one of the treatment option in radiotherapy, an IGRT could be developed with the support of any modern imaging devices as listed in the reference (Matuszak et al., 2010), such as CT scan, ultrasound, or diagnostic X-ray. As it has been referred, IGRT is a good radiotherapy technique to improve the motion error during radiotherapy, thus the possibility to improve better treatment outcomes for breast cancer will be possible by adding an IMRT system with modern imaging devices.

The option for VMAT also favorable over IMRT, since VMAT is an improved method from IMRT, some comparison studies also show that VMAT is better than IMRT in delivering conformal beams to some cancer sites, such as breasts (Qiu et al. 2010), head and neck (Hall and Phil, 2006), and prostate cancers (Ruben et al., 2008). In the case of breast cancer, other studies stated that VMAT is useful to reduce the radiation dose of significant organs around the breast such as lung and heart (Popescu et al., 2010).

In addition, brachytherapy has been used for cancer treatment in few hospitals. The treatment cost using brachytherapy eventually is lower than treatment cost using VMAT and IMRT. It means, brachytherapy can be used as one of treatment option in breast cancer.

One of Research Center in National Nuclear Energy Agency (BATAN), namely the Center of Radioisotope and Radiopharmaceutical has conducted research in order establishing brachytherapy seeds for servical cancer, as it has been stated in its Strategic Plans for the 2010- 2014 (PRR-BATAN, 2010). Regarding to this issue, there are many possibilities to develop the technology for breast cancer brachytherapy. Hence, it could lead to the low cost technology for breast cancer treatment without rely on foreign technology resources, which might increase the cost of radiotherapy. As a result, it will give more chance to the breast cancer patients to get access to modern radiotherapy.

Conclusion

To conclude, in regard to application of modern radiotherapy in Indonesia, Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Radiation Therapy (VMAT) can be used as the best option of favorable technique for breast cancer due to its abillity to reduce the radiation dose delivered to the organs at risk. Both techniques have been used in few hospitals in Indonesia. With these techniques, there will be possibility to develop technique to gain better treatment outcome in breast cancer. In addition, we are looking forward an established brachytherapy technology from the Center of Radioisotope and Radiopharmaceutical, with Ir-192 as one of options in breast cancer management in Indonesia.

References

Ahamad A. et al. (2005). Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue sparing effect to margin size. *Int J Radiat Oncol Biol Phys*, 2005, 62, 1117–1124.

Allen B., Marcu L., Bezak E. (2012). *Biomedical Physics in Radiotherapy for Cancer*. Collingwood: CSIRO publishing. pp. 394.

Anonimous, *Radiotherapy with Rapid arc – Website Siloam Hospital*. Retrieved October 22, 2012 from http://www.siloamhospitals.com/content/radiotherapy-rapidarc-mrccc-siloam-hospitals-semanggi.

Anonimous *Rapid Arc Overview-Oncology Treatment solution, Varian*. Retrieved October 19, 2012. from http://www.varian.com/us/oncology/treatments/treatment_techniques/rapidarc/.

Barton, M. B., Frommer, M., and Shafiq, J. (2006). Role of radiotherapy in cancer control in low-income and middle-income countries. *The Lancet Oncology*, 7(7), 584–595.

Bhide, S. A. and Nutting, C. M. (2010). *Recent advances in radiotherapy, BMC Medicine*, retrieved October 1, 2012 from http://www.biomedcentral.com/1741-7015/8/25.

Björk-Eriksson, T. and Glimelius, B. (2005), The potential of proton beam radiation therapy in breast cancer. *Acta oncologica* , 44, 8, 884–889.

Brans, B., Linden, O., Giammarile, F., Tennvall, J., and Punt, C. (2006). Clinical applications of newer radionuclide therapies. *European Journal of Cancer*, 42, 994-1003.

Center of Radioisotope and Radiopharmaceuticals (PRR) - National Nuclear Energy Agency Indonesia (BATAN). *Strategic Plans 2010-2014*, 15-20.

Chen, G. T. Y., & Sharp, Sharp. G. C., and Mori S.(2009). A review of image-guided radiotherapy. *Radiol Phys Technol*, 2, 1–12.

Dinesh Mayani, D.(2011). Proton therapy for cancer treatment. *Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners*,17, 3, 186–190.

Dowdell, S.J. et al. (2008). A comparison of proton therapy and IMRT treatment plans for prostate radiotherapy. *Australasian physical & engineering sciences in medicine*, 31, 4, 325–331.

Ferlay J., et al, (2010) GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide : IARC CancerBase No. 10, Lyon, France: International Agency for Research on Cancer. Available from: http://globocan.iarc.fr, accessed on 12/06/2013.

Fraass, B.A and Moran, J. M. (2012). Quality, technology and outcomes: evolution and evaluation of new treatments and/or new technology, *Seminars in radiation oncology*, 22(1), 3-10.

Georgakilas A.G. (2012). Cancer prevention – From mechanisms to translational benefits, Intech, Rijeka, 396.

Gomeziturriaga, A., et al. (2008), Early breast cancer treated with conservative surgery, adjuvant chemotherapy, and delayed accelerated partial breast irradiation with high-dose-rate brachytherapy. *Brachytherapy*, 7, 4, 310–315.

Hall J.E, and Phil D. (2006). Intensity Modulated Radiation Therapy, Protons, and the risk of second cancers. *International Journal of Radiation Oncology Biology Physics*, 65, 1, 1-7.

Herk, M.V. (2007). Different Styles of Image-Guided Radiotherapy, *Seminar in Radiation Oncology*, 258-267.

Hoskin P. (2012). *Radiotherapy in practice: External Beam Radiotherapy*, London: Oxford University Press, pp. 68.

Hoskin P.J. and Coyle C. (2011). Radiotherapy in practice:
Brachytherapy (1–20). London : Oxford University Press.

IAEA. (2008). Transition from 2-D Radiotherapy to 3-D Conformal and Intensity Modulated Radiotherapy. *IAEA TECDOC-1588* (pp 1-5). Vienna: IAEA Publication.

Inoue T. (2009). Current status and perspectives of brachytherapy. *Int Journal Clinical Oncology*, 14:1.

International Commission on Radiation Units and measurements (ICRU). (2010), Prescribing, recording, and reporting photon beam-IMRT. *International Commission on Radiation Units and measurements (ICRU) Report 83*. Maryland.

International Commission on Radiation Units and measurements (ICRU).(1993). Prescribing, recording, and reporting photon beam therapy. *International Commission on Radiation Units and measurements (ICRU) Report 50* (pp. 3-7). Maryland.

Khan, F.M. (2010). *Physics of Radiation Therapy* (pp. 413-515). Philadelphia: Lippincot William and WiIskin.

Kimman, M., Norman, R., Jan, S., Kingston, D., & Woodward, M. (2012). The burden of cancer in member countries of the Association of Southeast Asian Nations (ASEAN). *Asian Pacific journal of cancer prevention : APJCP*, 13(2), 411–420.

Lettmaier, S., Kreppner, S., Lotter, M., Walser, M., Ott, O. J., Fietkau, R., & Strnad, V.(2011). Radiation exposure of the heart , lung and skin by radiation therapy for breast cancer : A dosimetric comparison between partial breast irradiation using multicatheter brachytherapy and whole breast teletherapy. *Radiotherapy and Oncology*, *100*, 2, 189-194.

Levin, W. P., Kooy, H., Loeffler, J. S., and DeLaney, T. F. (2005). Proton beam therapy. *British journal of cancer*, *93*, 8, 849-54.

Levitt, S.H., Purdy J.A., Perez C.A., and Poortmans P. (2012). Technical Basis of Radiation Therapy. *Medical Radiology* (pp 253-256), *Radiation Oncology* (pp 617-618). Berlin: Springer.

Ling, C.C., Yorke, E., and Fuks, Z.(2006). From IMRT to IGRT : Frontierland or Neverland ?. *Radiotherapy and Oncology*, 78, 119-122.

Ludwig H., (1994). Women and cancer. *International Journal of Gynaecology & Obstetrics*, 46, 195-202.

MacDonald, S.M., DeLaney, T.F. and Loeffler, J.S. (2006). Proton beam radiation therapy. *Cancer investigation*, 24, 2, 199–208.

Macready, N. (2012). The promise of protons in cancer therapy, *Journal of the National Cancer Institute*, 104, 9, 648–9.

Matuszak, et al.(2010). Clinical Applications of Volumetric Modulated Arc Therapy. *International Journal of Radiation Oncology Biology Physics*, 77 (2), 608–616.

Mayles, A.Nahum and Rosenwald, J.C.(2007). *Handbook of Radiotherapy Physics : Theory and Practices* (pp 185). Florida: CRC Press.

Metcalfe P., Kron T. and Hoban P. (2007). *The Physics of Radiotherapy X-Rays and Electrons* (pp. 842). Madison :Medical Physics Publishing.

Nicolini, G., Clivio, A., Fogliata, A., Vanetti, E., & Cozzi, L. (2009). *Simultaneous integrated boost radiotherapy for bilateral breast : a treatment planning and dosimetric comparison for volumetric* *modulated arc and fixed field intensity modulated therapy*. Retrieved September 26, 2012 from http://www.ro-journal.com/content/4/1/27.

Otto K.(2008). Volumetric modulated arc therapy: IMRT in a single gantry arc. *Journal of Medical Physics* , 35, 310–317.

Podgorsak, E. B., & Kainz, K.(2006). Radiation Oncology Physics: A Handbook for Teachers and Students. *Medical Physics*, 33, 6.

Polgár, C. and Major, T.(2009). Current status and perspectives of brachytherapy for breast cancer. *International Journal of Clinical Oncology*, 14, 1, 7–10.

Popescu CC, et al. (2010). Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. *Int J Radiat Oncol Biol Phys*, 76, 287-295.

Proton therapy in the world. Retrieved October 22, 2012 from http://www.ptcs.ch/language/en-US/tabid/85/Home/Proton-Therapy/Proton-Therapy-worldwide.aspx.

Purdy J.A. (2001). *3D Conformal and Intensity Modulated Radiation Therapy: Physics and Clinical Applications* (pp. 1-15). Middleton: Advanced Medical Publishing, Inc.

Qiu JJ, et al.(2010). Impact of volumetric modulated arc therapy technique on treatment with partial breast irradiation. *Int J Radiat Oncol Biol Phys*, 78, 288-296.

Robinson, M.H.(2008). Radiotherapy : technical aspects, *Medicine*, 36(1), 9.

Ruben D.J. et al. (2008). The Effect of Intensity modulated Radiotherapy on Radiation Induced Second malignancies. *International Journal of Radiation Oncology Biology Physics*, 70, 5, 1530-1536.

Rudat V., Alaradi A.A., Mohamed A., Al-Yahya., and Altuwaijri S. (2011). Tangential beam IMRT versus tangential beam 3D-CRT of the chest wall in post mastectomy breast cancer patients: A dosimetric comparison. *Radiation Oncology*, 6-26.

Rulli, A., Barberini, F., Scialpi, M., Izzo, L., Angeli, I. D., Gori, S., Sidoni, A., et al. (2010). *Interstitial high-dose-rate brachytherapy after breast conserving surgery*, 417–422.

Ruther U, et al.(2000). *Secondary neoplasias following chemotherapy, radiotherapy and immune suppression. Karger, Basel, 162*. Retrieved August 19, 2011 from www.books.google.com.au.

Saphiro J. (2002). *Radiation Protection : A guide for scientists, regulator, and physicians, fourth edition* (145-146). Cambridge: Harvard University Press.

Spoelstra, F.O.B. and Senan, S.(2008). *Symposium article: Novel tools in radiotherapy, 19(Supplement 7),* 294–299.

Thariat J., et al. (2012). Radiotherapy and radiology: joint efforts for modern radiation planning and practice. *Diagnostic and Interventional Imaging*, 93, 342-350.

Walton, A., Broadbent A.(2008). Radiation- Induced Second Malignancies. *Journal of Palliative Medicine, Volume 11, No.10*, 1345-1352.

Weber, D.C. et al. (2004). A treatment planning comparison of intensity modulated photon and proton therapy for paraspinal sarcomas. *International journal of radiation oncology, biology, physics*, 58, 5, 1596–606.

WHO. *Cancer control : knowledge into action : WHO guide for effective programmes*. Retrieved September 27, 2012 from http : http://whqlibdoc.who.int/publications/2008/9789241547406_eng.pdf.

Williams and Thwaites. (1993). Radiotherapy Physics. *Oxford Medical Publications*, 1-7.

Yoon, M., et al. (2010). Radiation-induced cancers from modern radiotherapy techniques: intensity-modulated radiotherapy versus proton therapy. *International Journal of Radiation Oncology, Biology, Physics*, , 77, 5, 1477–1485.

Zelefsky, M. J., et al. (2012). Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. *International journal of radiation oncology, biology, physics*, *83*, 3, 953–959.