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Is there a place for quantitative risk assessment?

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Abstract

The use of ionising radiations is so well established, especially in the practice of medicine, that it is impossible to imagine contemporary life without them. At the same time, ionising radiations are a known and proven human carcinogen. Exposure to radiation in some contexts elicits fear and alarm (nuclear power for example) while in other situations, until recently at least, it was accepted with alacrity (diagnostic x-rays for example).

This non-uniform reaction to the potential hazards of radiation highlights the importance of quantitative risk estimates, which are necessary to help put things into perspective. Three areas will be discussed where quantitative risk estimates are needed and where uncertainties and limitations are a problem.

First, the question of diagnostic x-rays. CT usage over the past quarter of a century has increased about 12 fold in the UK and more than 20 fold in the US. In both countries, more than 90% of the collective population dose from diagnostic x-rays comes from the few high dose procedures, such as interventional radiology, CT scans, lumbar spine x-rays and barium enemas. These all involve doses close to the lower limit at which there are credible epidemiological data for an excess cancer incidence. This is a critical question; what is the lowest dose at which there is good evidence of an elevated cancer incidence? Without low dose risk estimates the risk–benefit ratio of diagnostic procedures cannot be assessed.

Second, the use of new techniques in radiation oncology. IMRT is widely used to obtain a more conformal dose distribution, particularly in children. It results in a larger total body dose, due to an increased number of monitor units and to the application of more radiation fields. The Linacs used today were not designed for IMRT and are based on leakage standards that were decided decades ago. It will be difficult and costly to reduce leakage from treatment machines, and a necessary first step is to refine the available radiation risks at the fractionated high doses characteristic of radiotherapy. The dose response for carcinogenesis is known for single doses up to about 2 Sv from the A-bomb data, but the shape at higher fractionated doses is uncertain.

Third, the proliferation of proton facilities. The improved dose distribution made possible by charged particle beams has created great interest and led to the design and building of many expensive proton centres. However, due to technical problems, most facilities use passive scattering, rather than spot scanning, to spread the pencil beam to cover realistic target volumes. This process, together with the methods used of final collimation, results in substantial total body doses of neutrons. The relative biological effectiveness of these neutrons is not well known, and the risk estimates are therefore uncertain. Unless and until the risks are known with more certainty, it is difficult to know how much effort and cost should be directed towards reducing, or eliminating, the neutron doses. These three examples, where uncertainties in quantitative risk estimates result in important practical problems, will be discussed.

1. Introduction

The title is in the form of a question to which there can be only one answer; a definitive YES. This is the only possible answer because we know from past experience that when intelligent and well-meaning people attempt to assess risks and make recommendations, the

consequences are usually good even when some of their data are inappropriate and their assumptions incorrect. For example, radiation protection has been an unqualified success over the last century. This can be illustrated by the study by Berrington *et al* [1] which followed the mortality of British radiologists between 1897 and 1997. There was an undoubted excess cancer incidence in the early years of the study as indicated by a standard mortality ratio (SMR) of 1.75 between 1897 and 1920. However, a later study by Carpenter *et al* [2] of a sub-set of these radiologists who were carefully compared with other physicians showed that in the years since World War 2, neither the SMR for cancer mortality nor that for overall mortality was significantly different from 1.0. What contributed to this desirable outcome? In 1956, the ICRP reduced the dose limit for radiation workers from 0.3 R/week to 0.1 R/week [3]. This amounts to 5 R/year, which is still the maximum permissible dose allowed to radiation workers in the US, except that the unit has changed to 50 mSv. This dose limit suggested by ICRP in 1956 was based entirely on genetic effects in the fruit fly, *Drosophila*. At that time the scientific committees involved in radiation protection introduced the concept of regulation of the overall average dose to the population and advanced the view that genetic hazards should be the main determinant for recommending limits of radiation exposure of people [4–6]. Although it was already well established that radiation could result in cancer induction and prenatal developmental defects, these were believed to occur only after large doses of 1–2 Gy.

The consensus view at the time can be summarised as follows [7];

1. Mutations, spontaneous or induced, are usually harmful. This we now know to be a wrong assumption since in fact few mutations turn out to be harmful.
2. Any dose entails some risk, i.e. there is no threshold.
3. The number of mutations is proportional to dose so that a linear extrapolation from high doses provides a valid estimate of low dose effects. (Here is the origin of the LNT hypothesis, which was introduced initially for genetic effects, not for cancer.)
4. The effect is independent of the rate at which the radiation is delivered or the spacing between fractionated exposures. This may be correct for *Drosophila*, but it is certainly not true for genetic effects in mice and presumably not true for humans either.

So we see that a wise decision was made to limit the maximum permissible radiation dose for workers, though the basis for the decision is suspect to say the least.

In the half century or so that has elapsed since that time the level of concern involving genetic effects, or heritable effects as we call them, has declined steadily, firstly because of the availability of mouse data and more recently with a reassessment of the importance of multifactorial diseases and doubt about the relevance of the specific locus mutations in mice [7]. As a consequence the percentage of radiation detriment attributed to the genetic component in the view of ICRP has declined from 100% in 1955, to 25% in 1977, to 18% in 1991 and to only 4% in 2007. In the meantime the level of concern involving radiation carcinogenesis has increased as more and more solid tumours have appeared in the Japanese A-bomb survivors. This trend is illustrated in figure 1. In the 1950s, genetic effects were considered to be most important, because solid tumours had not then appeared in large numbers in the A-bomb survivors. Over the years concern has switched entirely so that at the present time radiation carcinogenesis is considered to be by far the most important consequence of low doses of radiation [8]. Meanwhile, radiation protection standards have changed little.

2. Radiation carcinogenesis

Our knowledge of radiation-induced cancer comes from:

1. The A-bomb survivors [8–12].
2. Individuals occupationally exposed, such as nuclear workers [8].
3. Individuals medically exposed, including particularly second cancers in patients receiving radiotherapy [8, 13].

The study of the A-bomb survivors tells us several things:

1. Radiation-induced cancers appear at the same age as spontaneous cancers of the same type. This implies that most radiation-induced malignancies, with the exception of leukaemia, tend to occur late in life.
2. A careful study to estimate solid cancer risks from radiation takes more than 50 years.
3. The A-bomb study has cost the US taxpayer more than \$500 million to date, plus a contribution from the Japanese government.
4. For the reasons given above, there will never be a comparable study performed in the future.
5. The overall cancer risk at low doses and/or dose rates is about 5% Sv^{-1} .

The A-bomb survivor data tell us that the relative risk of solid cancers is a linear function of dose at least up to about 2 Sv [8–12]. These data allow estimates to be made of site-specific and gender-specific risk estimates for most of the radiogenic cancers, such as breast, thyroid, lung, colon stomach, liver etc [8]. The data also indicate clearly that the lifetime risk of cancer varies dramatically with age; while the average risk to the general population is about 5% Sv^{-1} , it is as high as 15% Sv^{-1} for a one year old female child, falling to about 1% Sv^{-1} for a 60 year old adult. Figure 2 shows how the A-bomb data represent the gold standard for risk estimates of radiation-induced cancer from about 0.2 to about 2.5 Sv. There is a linear relationship between risk and dose. Unfortunately most of our interest involves doses that are higher or lower than this range. Radiation oncology involves fractionated doses of 20 to 80 Gy, while doses in diagnostic radiology may be in the tens of mGy. In both cases there is considerable uncertainty as to whether the linearity, characteristic of the A-bomb survivor data, extends to these higher or lower doses, or whether the relationship becomes more complicated [13].

3. Radiation oncology

First, we will consider the high dose end. In most cases it is difficult to assess the risk of second cancers in radiotherapy patients because no good control group is available. There are some exceptions to this, such as cancer of the prostate and cancer of the cervix, where surgery is clearly an alternative. Another exception is Hodgkin's lymphoma where the risk of breast and lung cancer in young women is so obvious that a control group is hardly needed. Figure 3 shows the results of one of the largest studies ever performed to investigate second cancers in radiotherapy patients, in which 50 000 prostate patients receiving radiotherapy were compared with 70 000 who underwent a prostatectomy [14]. These patients, of course, were mostly elderly men in whom the overall incidence of second cancers after radiotherapy is about one-and-a-half per cent. It is interesting to note that, while many of the second cancers occur in organs close to the treatment field, as would be expected, such as the bladder and rectum, in fact about one third were induced in the lung, which is remote and receives a dose of about 2 Gy from scattered and leakage of radiation.

It is of considerable interest to ask what happens to the dose response curve for radiation carcinogenesis at the high fractionated doses characteristic of radiotherapy. Figure 4 shows data accumulated by Dr Elaine Ron of the NCI Epidemiological Branch for three types of tumours, where low dose data come from the A-bomb survivors and high dose data from radiotherapy patients [15]. It is evident from these data that at high doses the dose response curve tends to flatten off; it does not continue to rise as steeply as the A-bomb survivor data, nor does it fall off precipitously due to cell killing. A similar conclusion was reached by Sachs and Brenner [16] who studied the dose–response relationship for both breast and lung cancer in patients irradiated for Hodgkin’s lymphoma.

This information concerning the shape of the dose–response relationship for carcinogenesis at high fractionated radiation doses makes it possible to assess the impact of developments in radiation therapy which are designed to make the treatment more conformal, in the sense that radiation dose is concentrated in the target volume, while adjacent normal tissues are spared. This applies both to IMRT with x-rays and to the introduction of particle therapy with protons or carbon ions.

4. Intensity-modulated radiotherapy (IMRT)

Compared with conventional 3D conformal radiotherapy, IMRT results in an increase of monitor units by a factor of between 2 and 3. As a consequence the total body dose due to leakage radiation is increased by the same factor. In addition more treatment fields are usually used for IMRT and as a consequence a larger volume of normal tissue is exposed to lower doses. Several attempts have been made to estimate the impact of IMRT on the risk of fatal radiation-induced malignancies following radiotherapy for prostate cancer [17, 18]. The results are summarised in table 1. In general IMRT is estimated to approximately double the risk of second malignancies. In older patients, such as those being treated for prostate cancer, doubling the second cancer incidence may be acceptable if balanced by a big improvement in tumour control and reduced toxicity, since the incidence is quite low in the first place. The same may not be true of children, where the radiation-induced second cancer incidence is much higher. Doubling a much larger number may be unacceptable.

The problem of leakage radiation, which is exacerbated by techniques such as IMRT, can be readily mitigated by various means [15]:

1. Increased shielding could be added to the treatment head of the Linac; for example 10 or 20 cm of additional tungsten would reduce leakage by 90%.
2. The backup jaws could be made to track the multi-leaf collimator; this would further reduce leakage radiation since multi-leaf collimators leak 2–3% of the radiation beam.
3. The flattening filter is not needed for IMRT. Dispensing with it confers two benefits. First, it removes a source of scattered radiation, and second, it increases the dose rate to the iso-centre without increasing the leakage radiation.
4. Protons could be used in place of x-rays.

5. Protons

Because protons have a limited range and deposit most of their energy in the Bragg peak, protons represent the logical next step to improve those distributions, i.e. to maximise the dose to the tumour and minimise dose to normal tissues. At first sight one might expect that radiation-induced cancers outside the treatment volume should be essentially eliminated with protons because of the reduction in the volume of normal tissue exposed. However, this is not entirely the case because of the method commonly used to enhance the size of the

pencil beam of protons that emerges from a cyclotron or synchrotron to cover a tumour of realistic dimension.

The simplest way is to use passive scattering, allowing the pencil beam to impinge on a scattering foil, collimate the beam with a metal snout and finally shape the beam to the desired size and shape with a patient-specific collimator. The downside to this technique is that whenever protons lose energy they produce neutrons. The more sophisticated method is active scanning, using magnetic fields to scan the pencil beam of protons to cover the area required, and repeating this scan at each level through the tumour volume. However this is much more difficult and complicated to accomplish. These rival methodologies are illustrated in figure 5 [15]. The neutrons produced by passive scattering cover a wide range of energies and we do not have good information concerning their biological effectiveness. We know from the study of the A-bomb survivors that fission spectrum neutrons have an RBE that may be as high as 100, with a lower limit of 25 [19]. Many experiments have been performed with cancer in mice as the endpoint, which indicates that the RBE for fission neutrons is about 30 [20, 21]. With chromosome aberrations as an endpoint, the variation of RBE with neutron energy is well known; the RBE peaks at about 100 for low energy neutrons and falls steadily as the neutron energy increases [22]. Consequently we can make only a rough estimate of the RBE for the spectrum of neutrons produced in proton facilities using passive scattering. The best estimate is probably in the range 25–30.

In practice, while some neutrons are produced in the range modulator and the scattering foil, it turns out that the major contribution of neutrons comes from the treatment nozzle and the patient-specific final collimator. Largely for this reason, the neutron doses vary enormously between different facilities. This is illustrated in figure 6 [23–27]. This figure shows the neutron equivalent dose, as a function of distance outside the treatment field, for a number of proton facilities, and also the scattered and leakage x-ray dose for a typical IMRT set-up. It is evident that there is a wide range, with some proton facilities having much higher doses than IMRT while some have substantially less.

Brenner and Hall [28] estimated the lifetime second cancer risk from neutrons based on calculated neutron organ doses for a patient treated to 72 Gy for lung cancer at the Northeast Proton Therapy Center in Boston [29]. Using an estimated neutron RBE of 25, the second cancer risks are summarised in figure 7. Because the treatment plan considered involved the lung there is a big difference between female and male on this occasion because of the radiosensitivity of the breast in the case of the female. Since proton facilities cost of the order of \$125 million, it does not make sense to spray the patient with a total body dose of neutrons, the RBE of which is poorly known, and end up with a second cancer risk which is not much better than IMRT with a conventional Linac. The sophisticated solution to this problem is to use a scanning beam and avoid the problem of external neutrons altogether. However, this is technically difficult and introduces problems of its own, though most centres in the United States are planning to move in this direction. An alternative solution to the problem is to replace the final patient-specific collimator made of brass with a collimator made of material of lower mass number, since the neutron production cross-section is approximately proportional to mass number.

6. Diagnostic radiology

In the past, when cancer risks were available only at high doses and radiology procedures involved plane films, estimates of cancer risks from radiology required an extrapolation from high to low doses and assumptions about the shape of the dose–response relationship for carcinogenesis. That has changed a great deal in recent years. There are two reasons for this. First, the CT scans are now common and they involve much larger doses than plane

radiographs. Second, the maturing of the A-bomb data has provided cancer risks at lower doses than were previously available.

Figure 8 addresses the question of the lowest dose at which we have credible epidemiological data of an excess cancer risk. The dotted line is a linear extrapolation from the high dose A-bomb survivor data. The solid squares represent the lowest doses at which there is a statistically significant excess cancer risk in the A-bomb survivors. The lowest dose is around 30 to 40 mSv, which corresponds to several typical CT scans. These data are taken from the paper by Brenner *et al* (2003) in the *Proceedings of the National Academy of Sciences* [30]. The solid circle is the excess relative risk (ERR) for solid cancers taken from the 15 nations study of 600 000 nuclear workers by the International Association for Research on Cancer (IARC) published by Cardis *et al* [31]. In this case the average cumulative dose was 19.4 mSv and at this dose there is a statistically significant excess cancer risk. While the confidence intervals are large, the data are consistent with the low dose data from the A-bomb survivors. It must be admitted that there are some problems with this study that are yet to be worked out. The use of medical radiation for diagnostic purposes has increased dramatically in recent years to the point where the collective annual population dose from medical uses in the United States has increased by 750% in the last 25 years to its present value of about 930 000 personSv. (The collective population dose is the product of the dose and the number of individuals exposed to that dose.) [32] It is interesting and important to note that 90% of the collective dose from radiology comes from a limited number of high dose procedures which involve doses that are in the range where there is direct credible epidemiological evidence of an excess radiation-induced cancer incidence [33]. This is illustrated in figure 9. These high dose procedures include CT, nuclear medicine, interventional radiology plus small contributions from barium enemas and radiographs of the hip/pelvis. Only 10% of the collective dose comes from the millions of low dose procedures, such as chest x-rays or mammograms where to estimate the cancer risk would involve an extrapolation from high to low doses and an assumption about the shape of the dose–response relationship. Comparable data for the UK, though not as complete, are shown in figure 10 [34].

By 2006, the collective population dose in the UK had increased to approximately 21 800 personSv. If the size of the population is taken into account, the average dose per person from diagnostic radiology is very much smaller in the UK than in the United States. In both the US and the UK, almost half of the collective population dose from medical exposure comes from CT scans. In the UK, only about 15% of the population dose comes from medical exposures. By 2006 there were over 66 million CT scans performed in the United States, with about 6 million of them in children [33]. This is illustrated in figure 11. The use of CT scans is increasing just as rapidly in the UK as in the US, but again if the difference in population size is taken into account the number of scans per person per year is five times lower in the UK. The very rapid increase in the UK in the last few years is driven largely by the use of CT to diagnose appendicitis in young children, which until recently was not done in the UK, though it has been a common practice in the US for some years.

To estimate the risk associated with a particular procedure, such as a CT scan, the preferred method is to measure, or calculate, the dose to each organ as a function of age, gender and type of CT examination, apply cancer risk estimates specific for that organ, age and gender, available from the BEIR VII [8] report, but derived ultimately from the A-bomb survivor data and then to sum these risks for all organs exposed. This has been done for an abdominal CT scan, and the results shown in figure 12 [34]. What is plotted is the lifetime attributable risk of fatal cancer as a function of age from a single CT scan. It is evident that the risks are greatest by far for an infant, and decline rapidly with age. As a rule of thumb, an abdominal CT scan in a one-year-old child results in a lifetime cancer mortality risk of about one in a

thousand. Life is a risky business and in 1983 the Royal Society published an interesting commentary on risk [37].

It was pointed out that risks of about one in a million, or less, tend to be ignored and are quite acceptable in everyday life. This includes, for example, a flight on a commercial aircraft or driving to the airport. At the other extreme an annual occupational risk of death of one in hundred, as faced, for example, by coal miners in the 19th century, is totally unacceptable. Between these extremes, a risk of about one in a thousand or one in 2000, characteristic of an abdominal CT scan in a small child, is not unacceptable provided certain conditions are met.

1. The individual must be told of the risk.
2. The individual must receive some commensurate benefit.
3. It must be understood that everything reasonable has been done to minimise the risk. One might add, in the context of diagnostic radiology, one additional requirement not mentioned by the Royal Society ...
4. If NOT doing the procedure entails a greater risk.

On this basis, the time may come when it will be necessary to seek patient consent before doing a CT scan. When discussing the risks associated with diagnostic radiology, it is important to distinguish between individual risks and collective public health risks. The risk to the individual is always small, so that in a symptomatic patient the benefit–risk ratio is almost always very favourable. However, even a very small individual risk when multiplied by a very large and increasing number is likely to produce a significant long-term public health concern. For this reason it is important to try to reduce the dose associated with procedures such as CT scans, particularly in children, and to avoid altogether procedures when they are not absolutely necessary. It is in this spirit that the Royal College of Radiology discourages total body CT scans as part of routine health care, based on the report by COMARE [38].

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Figure 1.

Illustrating how, over the past half-a-century, the concern regarding exposure to ionising radiation has changed from heritable (genetic) effects to carcinogenesis. In 1950, based on mutations in the fruit fly *Drosophila*, heritable effects were considered to be the major risk of exposure to radiation. At that time, while an excess of leukaemia had been observed in the A-bomb survivors, solid cancers had not shown up. Over the years, concern for heritable effects has declined, but the maturing of the A-bomb data has revealed a significant excess incidence of a whole spectrum of solid cancers.

Figure 2.

Illustration of the dose–response relationship for radiation-induced carcinogenesis in humans. The atomic-bomb data represent the ‘gold standard,’ that is, the best quantitative data over a dose range from about 0.1 to 2.5 Gy. Considerable uncertainty exists above and below this dose range. At doses below this range, organisations such as the International Commission on Radiological Protection or National Council on Radiation Protection and Measurements, recommend a linear extrapolation from the high dose data; however, the bystander effect and the existence of radiosensitive subpopulations would suggest that this procedure would underestimate risks, whereas phenomena such as adaptive response suggest that a linear extrapolation would overestimate risks at low doses. Equal uncertainty exists concerning the dose–response relationship at high doses characteristic of radiation therapy. Does the risk continue to rise as a linear function of dose, does it plateau, or does the risk fall at higher doses because of cell killing? Adapted from [13].

Figure 3.

Top panel: percentage increase in relative risk for all solid tumours (except prostate cancer) for individuals who received radiotherapy for prostate cancer relative to the risk for individuals who underwent surgery for prostate cancer. Bottom panel: distribution of radiation-induced second cancer at 5+ years post radiotherapy. Illustration prepared by Dr David Brenner based on the data from Brenner *et al* [14].

Dose Response for Carcinogenesis at High Radiation Doses

Figure 4.

Excess relative risk as a function of dose for three types of radiation-induced human solid cancers. The low dose data (up to 2 Gy) came from the A-bomb survivors, while the high dose data refer to radiotherapy patients. Data compiled by Dr Elaine Ron [15].

How to scan pencil proton beams over a large target...

Figure 5.

Protons emerge from a cyclotron or synchrotron as a narrow pencil beam. To cover a tumour of realistic size, the pencil beam must be either scattered by a foil and then collimated, or scanned. Passive scattering is by far the simpler technique but suffers the disadvantage that it results in a total body neutron exposure. (Based on [15]).

Neutron Dose Equivalent vs. Distance from Field Edge

Figure 6.

Equivalent dose outside the treatment field for IMRT with x-rays and for various proton facilities. The data by Schneider *et al* are for a scanned beam. All other facilities involved passive scattering [23–27].

- ❖ For a 72 Gy proton therapy lung-tumor plan at the passively-modulated NPTC facility, assuming the patient is cured of his / her primary tumor.
- ❖ Doses derived from detailed Monte-Carlo simulations of the NPTC beamline by Paganetti and colleagues
- ❖ RBE assumed: 25

Figure 7.

Total estimated lifetime second cancer risks due to externally produced neutrons, for a 72 Gy proton therapy lung-tumour plan at the passively modulated NPTC facility, assuming the patient is cured of his/her primary tumour. Organ doses were calculated by Jiang *et al* [29] and the second cancer risk calculated by Brenner and Hall [28].

Figure 8.

Solid squares: estimated excess relative risk (± 1 SE) of mortality from solid cancers among groups of survivors in the lifespan cohort of atomic-bomb survivors who were exposed to low doses of radiation. The groups correspond to progressively larger maximum doses, with the mean doses in each group indicated above each data point. The lowest mean dose at which there is a statistically significant excess cancer risk is 3.5 rad (35 mSv). Data from Brenner *et al* [30]. Solid circle: estimated excess relative risk of mortality from solid cancers in the 15-nation study of nuclear workers. The average dose was 19.5 mSv (1.95 rad). Data from Cardis *et al* [31]. The dashed straight line is a linear extrapolation from the high dose data.

US Collective Dose (2006)

970,000 Person Sv

Figure 9.

Collective effective population dose due to diagnostic radiology and nuclear medicine in the United States for the year 2006. The millions of low dose procedures such as chest x-rays and mammograms account for only 10% of the collective dose. 90% of the collective dose comes from high dose procedures, such as CT scans, nuclear medicine, interventional radiology, examinations of the pelvis or hips and barium enemas, where the radiation doses are in the range where there is credible evidence of an excess cancer incidence based on the A-bomb survivors. Data from Hall and Brenner [33].

Collective Population Dose in the U.K. from High Dose Radiological Procedures

Figure 10.

Showing the increase with time of the collective population dose in the UK from radiological procedures. More than half comes from CT. Data from Brenner and Hall [34].

Figure 11.

Graphs illustrating the rapid increase in the number of CT scans per year in the UK and in the US, as well as the number of CT scans per person per year. Note that the number of scans per person per year is about five times lower in the UK than in the US. (From Hall and Brenner [33].) Data taken from [35, 36].

Figure 12.

Estimated age dependent, gender-averaged percentage lifetime radiation-attributable cancer risks from a typical single CT scan of the abdomen based on estimated organ doses. The methodology used is summarised in the text. The risks are highly age dependent, both because the doses are age dependent and because the risks per unit dose are age dependent. Data from Brenner and Hall [34].

Table 1

Estimated risk of fatal radiation-induced malignancies after RT for prostate cancer (% Sv^{-1}). (Abbreviations: IMRT = intensity-modulated radiation therapy; MV = megavoltage; RT = radiation therapy.)

Hall and Wu [17]	
Conventional 6 MV	1.5
IMRT 6 MV	3.0
Kry <i>et al</i> [18]	
Conventional 18 MV Varian	1.7
IMRT 6 MV Varian	2.9
Siemens	3.7
IMRT 10 MV Varian	2.1
IMRT 15 MV Varian	3.4
Siemens	4.0
IMRT 18 MV Varian	5.1