Contributions and Risks of Radiation Therapy in Managing Cancer During Pregnancy

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Introduction

Radiation therapy plays an important role in the treatment of most malignancies diagnosed during pregnancy, including breast cancer, cervical cancer and Hodgkin's lymphoma [1]. However, physicians are often hesitant to apply radiotherapy in pregnant women because of concerns about foetal safety. The risk for the unborn child after in utero irradiation depends on the radiation dose as well as on the stage of pregnancy. The International Commission on Radiological Protection (ICRP) reports on estimated foetal risks based on results of animal studies, data from survivors of nuclear explosions, data on children who were exposed to radiation in utero as a result of the Chernobyl accident and data from children exposed in utero to diagnostic X-rays [2]. Recently, Amant et al. [3] were the first to perform tests on general health, neuropsychological functioning and cardiac outcome in a group of children who were exposed to radiation therapy antenatally.

This chapter provides an overview of the knowledge on risks for the foetus, and recommendations are given for the administration of radiotherapy in pregnant women.

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Risks Associated with Foetal Exposure to Irradiation

Table 4.1 [1] gives an overview of estimated foetal risks after exposure to irradiation.

Two categories of effects of exposure to radiation can be distinguished: deterministic effects and stochastic effects. Deterministic effects are dose dependent: the severity of the effect depends on the dose given, and the effect occurs only above a certain threshold. The severity of stochastic effects, however, does not depend on the dose given, a threshold does not exist, but the probability of the effect to occur is dependent on the dose [4]. These effects are also referred to as teratogenic and carcinogenic effects, respectively.

Deterministic Effects

First Trimester

The first trimester is the period of organogenesis. During the first two weeks after conception, the number of cells is small and their nature is not yet specialized. Exposure to radiation is likely to result in failure to implant or death, resulting in spontaneous abortion [4]. From the third week after conception, malformations may be induced. The threshold for the occurrence of malformations is 100–200 mGy. This threshold is usually not reached with diagnostic procedures, but can be reached with radiotherapy. At this threshold, the risk of malformations is low, but the risk increases with increasing dose [4]. From 8 weeks after conception, the central nervous system is sensitive to radiation exposure. This is described in more detail below [4].

Table 4.1 Effects and risks after exposure to ionizing radiation in utero and spontaneous frequency (without exposure)

Time after conception (weeks	Effect	Risk per 0.01 Gy	Spontaneous frequency
0–2	Prenatal death[a]	0.01–0.001	0.3–0.6
3–8	Malformation[a]	0.005[b]	0.06
8–15	Mental retardation IQ decrease[c]	0.004	0.005
16–25	Mental retardation IQ decrease[d]	0.001	0.005
0–38	Leukaemia, solid tumours in childhood	0.003–0.004	0.002–0.003

Data taken from [1]

[a]Based on experimental data

[b]Above threshold dose of 0.1–0.2 Gy

[c]Reduction of 21 IQ points per 1 Gy above threshold of about 0.05 Gy; threshold dose for mental retardation about 0.06 Gy

[d]Reduction of 13 IQ points per 0.1 Gy above threshold dose of about 0.05 Gy, threshold dose for mental retardation 0.25 Gy

Second and Third Trimesters

In the last part of the first and in the second and third trimesters, the central nervous system is being developed. It is sensitive to radiation exposure from 8 to 25 weeks after conception, mainly from 8 to 15 weeks post conception. Only above a threshold of 50 [1]–100 [4] mGy, an effect on the central nervous system has been described. The main effect is a decrease of the intelligence quotient (IQ). This effect is dependent on foetal age and increases with increasing dose above 100 mGy. In the most sensitive period of the central nervous system, from 8 to 15 weeks after conception, a foetal dose of 1000 mGy (1 Gy) reduces the IQ by 20–30 points [1, 4]. The probability of mental retardation is about 40 % with this dose in this period of gestation [4]. The threshold for mental retardation is 250 mGy [1]. From 16 to 25 weeks of gestation, the risk of IQ decrease and mental retardation decreases. In this period, the risk of mental retardation is 0.1 % for every 10 mGy, and every 100 mGy above the threshold reduces the IQ with 13 points (Table 4.1) [1]. After 25 weeks of gestation, this effect is not seen. When informing a patient on these risks, it is important to relate the magnitude of radiation effects to the magnitude of spontaneously occurring abnormalities. Severe mental retardation occurs spontaneously in about 0.5 % of births. This incidence increases with a number of environmental factors, such as malnutrition, maternal alcoholism and rubella infections during pregnancy [4]. Figure 4.1 summarizes the effects of prenatal irradiation on the foetus [5].

Stochastic Effects

The main stochastic effect of radiation exposure to a foetus in utero is the induction of childhood cancer and leukaemia. It is assumed that the unborn foetus is at the same risk for potential carcinogenic effects of radiation as are children.

The spontaneous incidence of childhood cancer and leukaemia (ages 0–15 years) is 0.2–0.3 %. At low doses, this incidence does not seem to increase. Following a foetal dose of about 10 mGy, the relative risk is maximum 1.4. This means that the probability of childhood cancer remains low (0.3–0.4 %) [4].

A second stochastic effect is the induction of genetic mutations to the oocytes in case of preconceptional irradiation. In mice, mature oocytes are more radiosensitive than immature oocytes. In humans, no heritable effects that would be linked to parental radiation exposure have been described. However, based on the mice studies, it is often recommended that pregnancy should be delayed several months to 1 year after radiation treatment out of safety concerns [4]. This should be weighed to other considerations such as the age of the women and therefore not be an absolute criterion by itself.

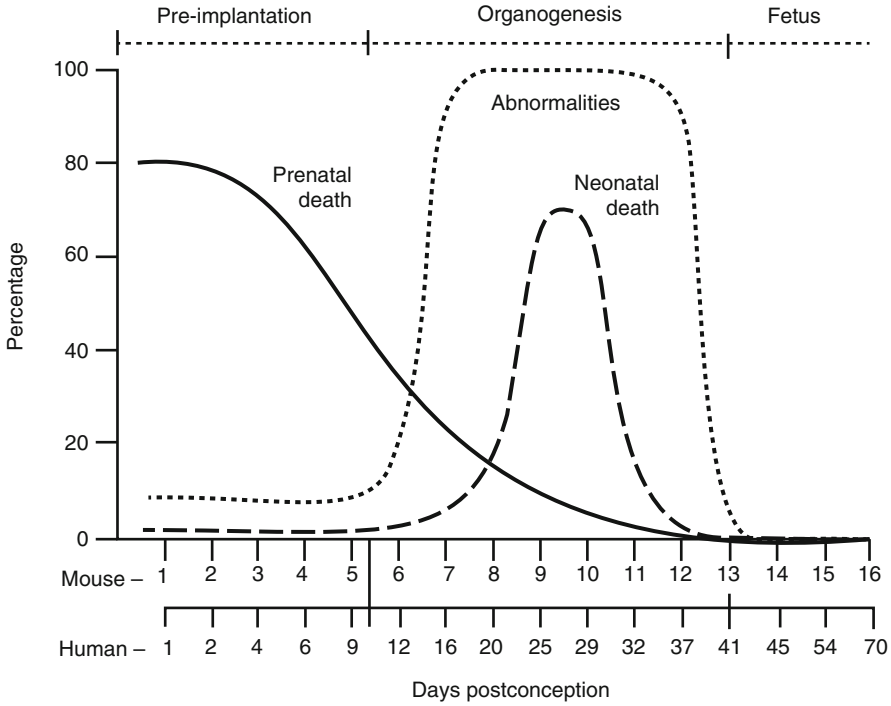

Fig. 4.1 The occurrence of lethality and abnormalities in mice after a prenatal radiation exposure of about 2 Gy, given at various times post conception. The two scales for the abscissa compare developmental stages in days for mice and humans (Redrawn from Hall 1994 [5] with permission of E. Hall and the publisher)

Consequences of Foetal Risks of Radiation Exposure from Radiation Therapy

In pregnant women, as in any other patient, the benefits and disadvantages of a radiation treatment should be weighed carefully. However, this can be much more complicated due to the fact that the foetal risk also has to be considered. The ICRP advises that in case of a pregnant patient, factors that should be considered include [4]:

- The stage and aggressiveness of the tumour
- Other various therapies and their length, efficacy and complications
- Impact of delaying therapy
- Stage of pregnancy
- Expected effects of maternal ill-health on the foetus
- Foetal assessment and monitoring
- How and when the baby could be safely delivered
- Whether the pregnancy should be terminated
- Legal, ethical and moral issues

Besides these issues, the distance from the target volume to the foetus should be considered, as this gives an indication of the expected exposure of the foetus to radiation. If the foetus is either in or very close to the target volume, the effects on the foetus are severe and usually lead to foetal death. Radiotherapy can therefore not be given to the pelvic region during pregnancy.

Radiation therapy can certainly be considered during pregnancy when the target volume lies outside the pelvis. In order to be able to estimate the foetal risk, an estimation of the foetal dose should be made. The fact that the uterus grows during the radiation treatment may decrease the distance of the foetus to the target volume. This should be taken into consideration when estimating the foetal dose. For example, when giving breast or chest wall irradiation during early pregnancy, the embryo will be exposed to 0.1–0.3 % of the dose given (50–150 mGy with a prescription dose of 50 Gy) [1], which carries a very low supplementary risk of malformations (Table 4.1). Whereas, towards the end of the pregnancy, the dose to the foetus can exceed 2 Gy. However, radiation-induced congenital abnormalities are extremely rare in case of exposure after organogenesis [4]. During this period, the main risks for the unborn child are a lower IQ and a risk of radiation-induced malignancies for the child after exposure to radiation in utero [4]. Amant et al. reported on an International Consensus Meeting that was held on treatment of breast cancer during pregnancy. After extensive discussion, the participants agreed that radiation therapy during the first and second trimesters carries relatively low foetal risk, but that radiation therapy should be avoided in the third trimester because of the related significantly higher foetal dose [6].

Attempts should be made to decrease the foetal dose as much as possible, for example, with additional shielding. When the foetal risk is acceptably low, the radiation treatment should be given when this provides a beneficial effect for the patient. This was confirmed by recent findings of the group of Amant [3]. They performed neurological examination, tests to investigate cognitive functioning, questionnaires on general health and echocardiographic evaluation in 16 children (median age 6 years, range 1.5–9) and 10 adults (median age 33 years, range 22–49) who had been exposed to radiation therapy in utero. Median dose to the mother was 48 Gy (range 12–70 Gy) and median foetal dose was 91 mGy (range 0–1690 mGy). They reported that neuropsychological, behavioural and general health outcomes were within normal ranges. There was no linear relationship between foetal dose and cognitive outcome. In one child, there was a severe cognitive delay; however, in this case, foetal dose was relatively low (34 mGy), and there were other complications during pregnancy that may explain this delay, such as preterm delivery.

When the estimated foetal risk seems high, other treatment options, or reversing the sequence of treatment modalities, should be considered (e.g. administration of chemotherapy first, in order to delay radiation treatment until after delivery). Ultimately, termination of the pregnancy or early delivery can be considered. It is of utmost importance that the pregnant patient and her partner are involved in this decision-making process. They should be carefully informed about the benefits and disadvantages of all options for the patient as well as of the unborn child. Shared decision making should be pursued in all cases [1, 4].

Calculation and Measurement of the Dose to the Foetus

During external beam radiation therapy, the patient receives dose outside of the primary radiation field. We use the term peripheral dose in this chapter, although sometimes it is also referred to as the out-of-field dose.

Contributions to the Peripheral Dose

Contributions to the peripheral dose originate from several causes, as illustrated in Fig. 4.2 [7, 9]:

1. Leakage radiation through the treatment head of the accelerator
2. Radiation scattered from the collimator and beam modifiers
3. Radiation scattered from the floor, walls or ceiling
4. Radiation scattered in the patient or internal patient scatter

Leakage Radiation

According to standards set by the International Electrotechnical Commission for medical electrical equipment (IEC 601–2–1 1981), the leakage dose outside the radiation field at 1 m from the beam axis should be less than 0.1 % of the dose inside the beam. Measurements have shown that in reality, the leakage dose is well below this 0.1 % value and that the variation between linear accelerator brands and energies is small [8]. During acceptance of a new accelerator, the physicist should always measure the radiation leakage. The measurement will contain some scattered radiation as well, so the true leakage value will be smaller than the actual measured value. According to Stovall et al. [9] in their report of the American Association of Physicists in Medicine (AAPM) Task Group 36, leakage becomes the main contributor at greater distances from the field edge.

Radiation Scatter from the Collimator and Beam Modifiers

Radiation scattered from the collimator and beam modifiers depends on the collimator design: the collimator jaws and flattening filter. Measurements in large water phantoms for older accelerators show average collimator-scattered radiation values of about 0.35 % of the central axis dose maximum for a 20×20 cm^2 field at 30 cm distance [6, 8]. In addition, the collimator-scattered radiation dose is lowest for 6 MV photon beams, about 10 % lower than for 10 MV beams and 30 % lower than for 23 MV beams. For photon energies larger than 15 MV, neutrons are a significant contributor to the out-of-field dose [10]. Just outside the beam, the collimator scatter contributes 20–40 % of the total peripheral dose [7]. Older literature (e.g. [9, 11]) also mentions the peripheral dose increase through the use of wedges, by a factor of 2–4. The use of physical wedges should thereby be avoided for pregnant patients. The use of dynamic (Varian) or universal wedges (Elekta) or the use of a secondary multileaf collimator (MLC) does not increase the peripheral dose [12, 13]. Field-in-field techniques, where small extra beams are used to obtain a homogeneous dose distribution, can also be used.

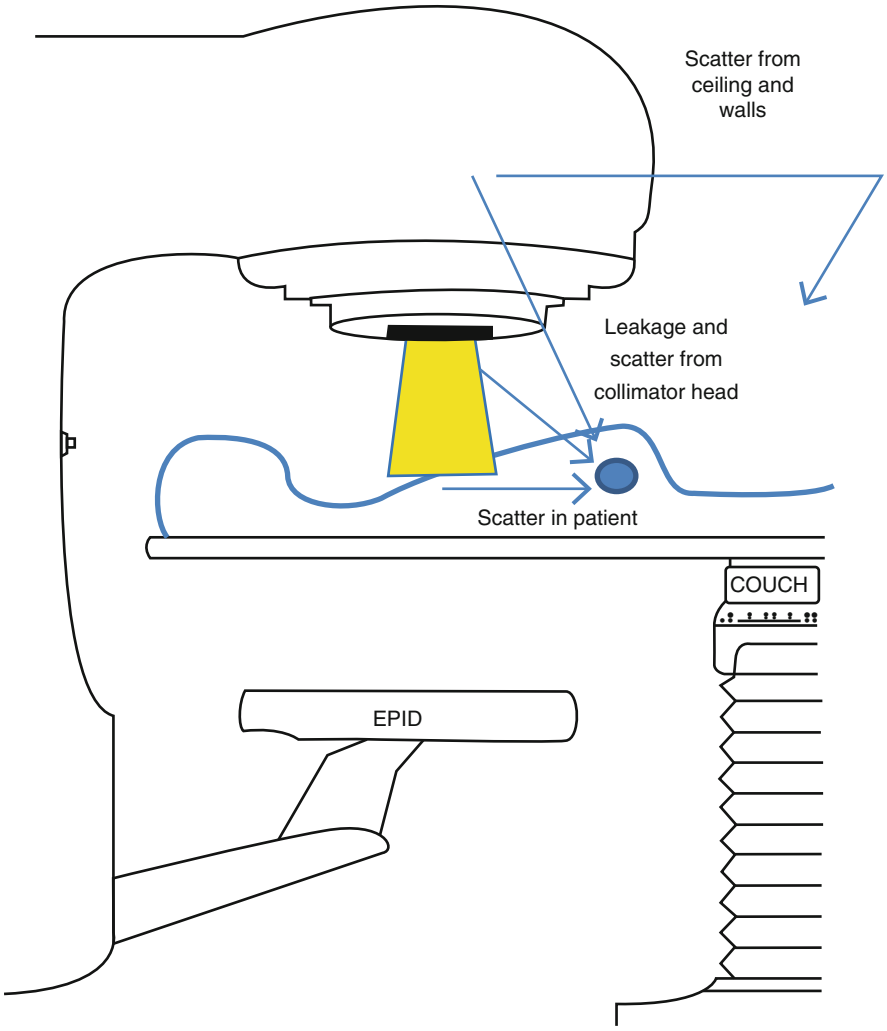

Fig. 4.2 Pathways of radiation contributing to the peripheral dose

The above described leakage and collimator-scattered dose can be reduced by placing a lead shield over the critical area. Measurements have shown that shielding can reduce the dose to the foetus by 50 % [9]. It is, therefore, advised to use proper and safe (mechanical) shielding, and if necessary refer the patient to a hospital with dedicated equipment and experience. Examples of shielding designs are given in the literature, e.g., [9].

It should be noted that shielding can only intercept the radiation from the head of the machine. Due to the high energy, shielding requires strong constructions carrying the heavy shielding material such as lead sheets. Four to five half-value layers of lead correspond to approximately 5–7 cm of lead or 6–8.5 cm of Cerrobend [9].

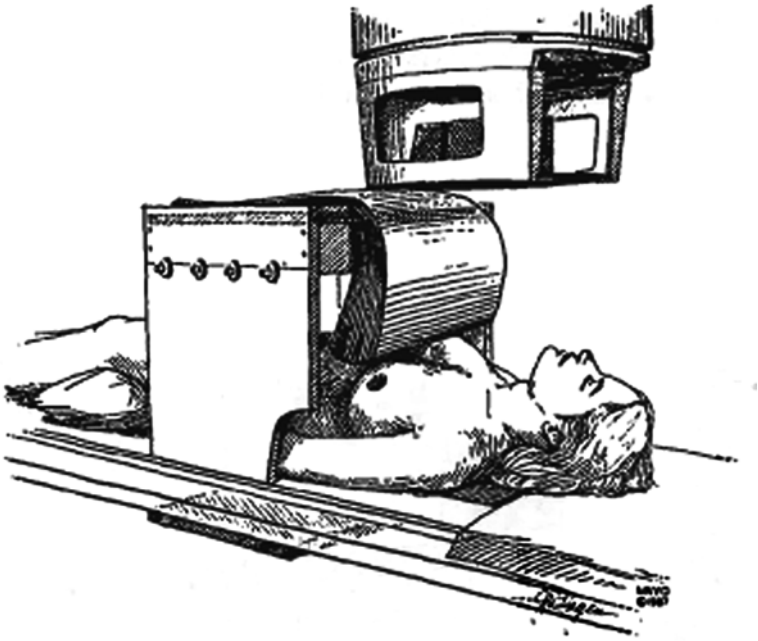

Fig. 4.3 Example of a shielding bridge with the patient in treatment position (Taken from: AAPM Report No. 50. AAPM Task Group 36, 1995 [9] with permission of AAPM)

Both constructions with a bridge placed over the patient on the treatment table, as well as mobile shields, are described in the AAPM TG-36 report. An example is shown in Fig. 4.3. For tangential field set-ups, the shielding design should allow protection for both the medio-lateral and the latero-medial beam directions.

Radiation Scattered from the Floor and Walls

The third origin of peripheral dose is the dose scattered from the floor, walls or ceiling, which is only described in very few papers (e.g. [14]) and which is one or two orders of magnitude lower (about 0.01 % for 6 MV) than the collimator leakage and scatter.

Radiation Scattered in the Patient

The final source of peripheral dose is the radiation scattered in the patient. The dose scattered in the patient increases with increasing irradiated volume, so both are with field size and patient thickness in the primary beam. Patient scatter rapidly decreases, approximately exponentially, with increasing distance from the field edge, from a few per cent of the primary beam dose very close to the field edge to about 0.01 %, at 30–80 cm from the beam axis, depending on the field size [14].

Patient scatter is the main contributor to the peripheral dose near the field edge (more than 80 % at distances up to 10 cm from the field edge), while leakage

radiation is the major contributor at large distances from the field edge (more than 80 % at distances from 50 cm from the field edge). At about 10 cm from the field edge, the dose is about 1 % of the central axis beam dose, more or less independent of energy and depth, but increasing from 0.5 % for a 5×5 cm^2 field to 2 % for a 25×25 cm^2 field [9].

Calculation of Peripheral Dose

Dose calculation algorithms and treatment planning systems (TPS) are designed to ensure a high-accuracy dose delivery at the target volume in the patient. Therefore, the dose calculation is generally very accurate inside the treatment field, even in the presence of inhomogeneities, but outside the field, where the delivered dose is very low, still large uncertainties in dose calculations may be present.

Calculation of Peripheral Dose for Conventional Radiotherapy Techniques

Due to the lack of accurate data and the observed inaccuracies in treatment planning beam modelling in out-of-field regions, Van der Giessen in the 1990s [8, 14] collected and published many data sets of various beam energies and accelerator models in dependence on distance, field size and depth in large water phantoms. An example of these data is shown in Fig. 4.4 with the peripheral dose for a number of field sizes expressed as a percentage of the maximum central axis dose vs. distance from the beam axis. The data were modelled in a freeware software programme called Peridose for the radiotherapy techniques at that time. However, this programme was written for conventional radiotherapy techniques with linear accelerators and cobalt-60 equipment only.

Calculation of Peripheral Dose in Modern Radiotherapy Techniques

These data and other literature concerning peripheral dose were published before the introduction of the present state-of-the-art treatment techniques, using virtual wedges, intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT, Elekta) or RapidArc (Varian). For these treatment techniques, the number of monitor units (MUs) required to obtain an adequate dose distribution might be increased significantly, resulting in an increased peripheral dose as a result of collimator leakage and collimator-scattered dose.

In 2013 Huang et al. compared dose measurements and calculations outside the treatment field for several IMRT plans, calculated using the Pinnacle v9.0 treatment planning software [15]. With increasing distances from the field edge, the dose decreases, but the underestimation of the measured dose by the treatment planning system (TPS) becomes larger, with an average underestimation of the dose by the TPS of 50 % at 15 cm and of 80 % at 30 cm. More or less the same underestimation of the dose by the TPS was found by Howell et al. for a simple mantle field calculated with Eclipse (Varian) [16]. It is clear that the medical physicist should model the beam in the TPS with great care during the commissioning phase, not only

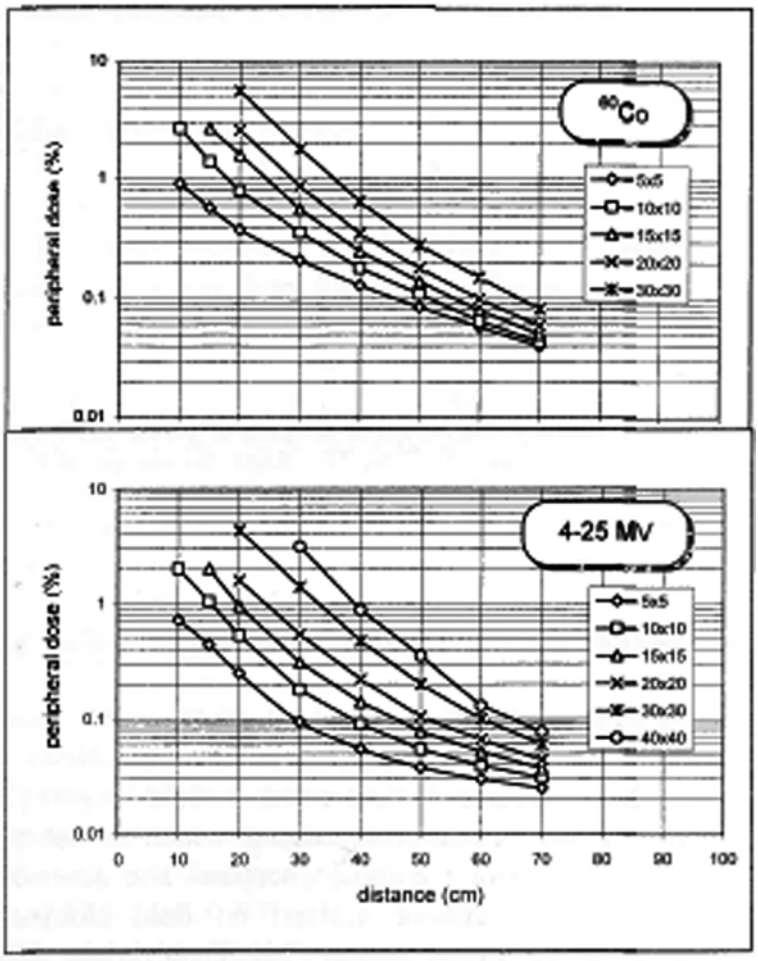

Fig. 4.4 Total peripheral dose in percentage of the central axis maximum dose as a function of distance for a number of field sizes (Taken from P.H. Van der Giessen, Thesis Leiden University 1997, with permission of the author)

paying attention to the beam profiles in the central area and penumbra but also to a sufficient large distance outside the penumbra. If the TPS is modelled well and if the distances to given points or structures (e.g. representing the foetus) are reasonably near to the target volume, dose volume histograms can be used for a good estimate to those points or structures. With increasing distance, the uncertainties in those outcomes will increase.

Proper shielding might reduce leakage and collimator-related contributions to the peripheral dose, but the amount of shielding that has to be applied is considerable. Therefore, when the patient is pregnant, the advantages of IMRT or modern arc therapies should be weighed against the increased dose to the foetus.

Image-guided radiotherapy, where the patient positioning is checked and corrected for during each treatment session, has become very common in modern radiotherapy departments. The treatment position is checked on-line (images taken every day) or off-line (e.g. imaging during the first few fractions and repeat images every week) using orthogonal MV images, orthogonal kV images, or cone-beam CT (CBCT). ICRP Publication 129 [17] estimates typical absorbed doses between 1 and 40 mGy when obtained with kV CBCT. MV CBCT with beam energies up to 6 MV shows typical absorbed doses between 20 and 100 mGy. It is noted that the imaging volumes can be significantly larger than the target volume of the radiotherapy course. Such repeated exposures are not included in the calculated peripheral dose estimates by the TPS, but they do add up to the total absorbed foetal dose. For pregnant patients, it is therefore recommended to limit the image fields and to apply orthogonal kV images to obtain the lowest possible addition to the total peripheral dose as a result of imaging.

Measurement of Peripheral Dose

The total dose outside a field can be measured in a phantom, either in a water tank, a solid polystyrene phantom or an anthropomorphic phantom. Ionization chambers, diodes or thermoluminescent dosimeters (TLDs) are suitable instruments. If specific shielding for the pregnant patient is available, the measurement can be performed with and without the shielding thus showing the dose reduction. Points of measurement should be sufficient to determine the range of dose to the foetus. The AAPM report [9] recommends to compare measurements at representative points outside the beam in a phantom with specific points at the surface of the phantom, to be able to correlate these data to foetal dose when monitoring at points on the patient, e.g. the fundus, symphysis pubis and umbilicus.

For in vivo measurements, the daily doses may be relatively small. Therefore, the medical physicist should ensure that the dosimeters measure accurately at these low dose levels.

Peripheral Dose with CyberKnife and Helical Tomotherapy

Chuang et al. [18] investigated the peripheral dose for a brain and thorax treatment to an anthropomorphic phantom with a CyberKnife unit after upgrading of the accelerator shielding. The results demonstrated that the additional shielding decreased the peripheral dose on this unit by a maximum of 59 % at 30 cm from the field edge to a value comparable to that measured for other treatment modalities. For distances between 30 and 70 cm from the field edge, the CyberKnife peripheral dose remained higher than doses measured in a previous study of the authors on IMRT.

Ramsay et al. [19] measured peripheral doses in-phantom using a helical tomotherapy system which is designed to deliver highly conformal intensity-modulated radiation therapy (IMRT). The concern of the authors was a possible increase of whole body dose due to increased leakage radiation as a consequence of the

relatively long treatment times of the equipment. The investigation showed that the delivery system was designed to maximize shielding for radiation leakage. As such, the peripheral doses are equal to or less than the published peripheral doses for IMRT delivery on other linear accelerators. This study, as does the one from Chuang et al. [18], indicates that peripheral dose values of higher or at best similar magnitude are obtained with these specific treatment delivery units compared to conventional linear accelerators. As such, at least similar shielding requirements should be considered compared to linear accelerators.

Radiotherapy with Heavy Particles during Pregnancy

There is much less experience with heavy ion radiotherapy during pregnancy. We can only cite from a few case studies. Tachibana et al. report a case of heavy ion radiotherapy to a lung metastasis of a sarcoma to a dose of 57 Gy. Foetal dose (equivalent) was 35 mSv, and a healthy baby was delivered [20]. Another group reports on a successful radiation treatment with carbon ions to a skull-base chordoma. Dose to the uterus was <0.2 mSv. Also in this case, a healthy baby was delivered [21].

Step-By-Step Delivery of a Treatment Plan in a Pregnant Patient

The AAPM provided a series of recommendations [9] which have been taken over by the ICRP in their report on radiotherapy during pregnancy [4]. These are listed here in a modernized form for present-day equipment (e.g. radiographic films for position checks are rarely used nowadays):

- Complete all planning as usual. If the foetus is situated near the treatment beam, avoid using large-field imaging or CBCT.
- Consider modifications to the treatment plan that would reduce the radiation dose to the foetus by changing field size, angle, radiation energy and beam modifiers such as blocks and wedges. Photon energies above 10 MV should be avoided.
- Estimate dose to the foetus without special shielding, using out-of-beam phantom measurements at the symphysis pubis, fundus and a midpoint.
- The AAPM recommends using shielding if foetal dose is above 50–100 mGy, with 4–5 half-value layers of lead. Measure dose to foetus in a phantom or simulated treatment with the shielding in place, adjusting radiation amount and location.
- Document the treatment plan and discuss it with the staff involved in patient set-up. Document the shielding.
- Check weight- and load-bearing specifications of the treatment couch or other aspects of shielding support.
- Be present during the initial treatment to assure that shielding is correctly placed.
- Monitor foetal size and growth throughout the course of treatment and reassess foetal dose if necessary.

- At completion of treatment, document total dose including range of dose to the foetus during therapy.
- Consider referring patient to another institution if equipment and personnel are not available for estimating and reducing the foetal dose.

We suggest adding the following recommendations:

- During commissioning of the TPS, take special care in accurately measuring the peripheral dose to a distance of at least 10 cm from the field edge and also compare measurements (preferably also with TLD) and calculations at distances of 5, 10, 15 and 20 cm from the field edge.
- If possible, use the lowest beam energy (often: 6 MV), since the peripheral dose is lowest for this energy and no neutrons are generated [6].
- Use optimized treatment plans with as little MUs as possible.
- Use kV imaging for image guidance, and limit the field size as much as possible instead of using MV imaging or CBCT.

Pregnancy Termination

In some cases, termination of the pregnancy might be considered. This, of course, is an individual decision. For foetal doses under 0.1 Gy, termination of the pregnancy does not seem medically justified. From studies in animals and from data on survivors of the nuclear explosions in Japan, it can be derived that at foetal doses, this low, foetal risk is negligible. In these studies, this dose was delivered in a single fraction. Therefore, with multiple fractions as delivered in clinical circumstances, the foetal risk at foetal doses of under 0.2 Gy seems to be so low that termination of pregnancy might also not be justified with foetal doses of 0.1–0.2 Gy. As was shown in the previous sections, foetal dose does generally not exceed this threshold when a tumour site at a distance from the uterus is being irradiated.

With higher doses, the foetal risk increases. Depending on the gestational stage, the foetus is at risk of developing malformations or IQ reduction (Table 4.1). In the case of substantial foetal risk, termination of the pregnancy can be considered, after carefully informing the parents on the significance and extent of this risk [3].

Conclusion

In pregnant patients, malignancies that are outside the pelvis and abdomen can generally safely be treated with radiotherapy. However, every case needs to be individualized depending on the type of cancer, stage of the disease and gestational stage. Other treatment options or a different order of treatment modalities should be considered. Doctor-patient shared decision-making after carefully informing the patient and her partner should be pursued. When the best option seems to irradiate during pregnancy, precautions need to be taken to reduce the foetal dose as much as possible, in order to minimize the foetal risk.

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