COMPLICATIONS OF TREATMENT

Radiotherapy to patients with artificial cardiac pacemakers

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Summary
Background: The in vitro studies show that the modern cardiac pacemakers utilising the complementary metal-oxide semi-conductor (CMOS) circuitry can be adversely affected by therapeutic radiation. However, the published clinical data are sparse regarding the safety of radiotherapy delivery to patients with artificial pacemakers. Despite the potential risk of life threatening complications, there are no national guidelines and most radiotherapy departments have no formal clinical risk management strategy in place. A literature review was performed to assess the risks involved in irradiating patients with pacemakers and to identify strategies, which minimise the risk of pacemaker malfunction. Recommendations for radiotherapy departments are made.

Conclusion: Modern multi-programmable pacemakers are very sensitive to therapeutic megavoltage irradiation. There is no safe radiation threshold for megavoltage radiation. The low energy kilovoltage X-rays used for radiotherapy simulation cause no pacemaker malfunction. Megavoltage radiation can be safely delivered to patients with cardiac pacemakers provided direct irradiation of pacemakers is avoided, adequate monitoring is done during and after irradiation, and the dose to the pacemaker generator is kept below 2 Gy. Close liaison with cardiologists and a pacemaker clinic is essential and radiotherapy departments should have protocols in place to identify and care for cancer patients with pacemakers.

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KEYWORDS
Artificial pacemaker; Implantable defibrillators; Radiotherapy; Linear accelerators; Electromagnetic Fields; Radiation damage

Introduction

Even by conservative estimates, at least one million patients in USA have permanent artificial cardiac pacemakers and this figure could be in excess of five million worldwide.1–3 This number
is set to increase because of various reasons. Firstly, the life expectancy of the population, particularly in the West, has dramatically improved over the past century. For instance, the life expectancy has increased by more than 65% in England and Wales over the past century. One consequence of the increase in longevity is the increase in prevalence of cardiovascular morbidity. This in turn is leading to an increase in the number of patients with implanted permanent pacemakers. Secondly, the indications for artificial pacemaker insertion are expanding and the recent guidelines issued by the National Institute of Clinical excellence in UK and the American College of Cardiology reflect this trend.

Cancer, like cardiovascular disease, is mostly a disease of the elderly. The age-standardised incidence of cancer has increased by more than 25% in the past 30 years. It has been estimated that 50–60% of all patients with cancer will require radiotherapy at some point during the course of their illness. Consequently, with an ageing population the number of patients with pacemakers presenting to the radiotherapy department is increasing.

The older generation of pacemakers were made up of bipolar semiconductor devices and were fairly resistant to radiation damage. Hence delivery of radiotherapy, in the past, posed no significant clinical risk. By contrast, the modern programmable pacemakers are very sensitive to megavoltage radiation. This increased sensitivity is due to the complementary metal-oxide semiconductors (CMOS) circuits used in the manufacture of cardiac pacemakers over the past three decades.

In fact, electromagnetic interference from any source can adversely affect pacemaker function. Such interference from linear accelerators can inhibit or inappropriately trigger the pacemaker. In the future, it is likely that sources of electrical interference will steadily increase because of new accelerators features, such as beam gating, and the appearance of in-room accessories such as breathing control systems. Special care may also be required when using automatic set up since reduced time in the treatment room may potentially increase the patient risks. However one of the main risks is from therapeutic megavoltage radiation which can damage or destroy both the hardware and software components of the pacemaker.

Despite the potential risk of catastrophic complications, the published clinical data are sparse regarding the safety of radiotherapy delivery to patients with pacemakers. Most of the clinical data found on PubMed search are case reports of single patient. There are no reports of large case series and as far as the authors are aware, there are no ongoing prospective studies. There are no uniform recommendations from the manufacturers and the available recommendations are often unreliable. Most radiotherapy departments do not have a formal protocol in place to deal with patients with pacemakers. The American Association of Physicists in Medicine published guidelines in 1994 and in spite of the increasing sophistication of pacemaker technology over the past decade, there has been no other recent official publication of guidelines. Hence, we did a literature review analyzing the hazards associated with irradiation of patients with artificial pacemakers.

**Methods**

The online PubMed database (1966–2004) at the National Library of Medicine was searched using the following key words. Artificial pacemaker, artificial cardiac pacing, implantable defibrillators, X-rays, photons, ionising radiation, radiotherapy, linear accelerators, electromagnetic fields, equipment failure, radiation damage and radiation effects. The reference lists of selected articles were searched for articles not retrieved by database search.

**Overview of artificial cardiac pacemakers**

The concept of cardiac pacemakers as potentially life saving devices emerged in 1950s. Since the first pacemaker implant in 1958, the technology and clinical practice of cardiac pacing has evolved rapidly over the past four decades. It has been estimated that there are more than a million people with pacemakers in USA and these are being implanted at a rate of nearly half a million each year worldwide. Cardiac pacemakers are commonly inserted into a subcutaneous pocket over the anterior chest wall. The artificial pacemakers commonly pose a problem to the radiotherapists during the treatment of lymphomas, breast, lung, head and neck, thyroid and oesophageal cancers. In fact, management of these cancers often involves extensive use of radical as well as palliative radiotherapy. It has been estimated that up to 66% of patients with lung and breast cancers might require radiotherapy at some point during the course of the illness.
Radiotherapists will increasingly come across cancer patients with permanent cardiac pacemakers. Hence, we provide a brief overview of the normal electrical physiology of heart, types of cardiac pacemakers, clinical indications for pacemakers and potential sources of interference.

Normal electrical physiology of heart

The four chambers of heart, through rhythmic contractions, pump blood into the pulmonary and systemic circulations. The rhythmic contractions (heart beats) are initiated by electrical impulses generated intrinsically by the natural heart pacemaker. The intrinsic natural pacemaker of heart is resistant to therapeutic doses of radiation.

The sinoatrial node, situated in the right atrium, is the natural pacemaker of heart and generates the cardiac electrical impulse. This electrical impulse travels along three specialised bands of tissue to the atrioventricular node, which is situated at the junction of the atria and ventricles. From the atrioventricular node, the impulses travel through specialised conduction tissue in the ventricles called right and left bundle branches. From there the impulses then travel through the musculature of the ventricles thereby causing the ventricles to contract rhythmically and eject blood into the systemic (left ventricle) and pulmonary (right ventricle) circulation. The universally used ECG (electrocardiogram) is a vectorial description of these electrical impulses. Various cardiac diseases can disturb the normal electro-physiology of the heart. In case of dysfunction of the intrinsic pacemaker of the heart, artificial cardiac pacemakers can be used to restore and compensate the disturbances in pulse generation and propagation. Before the introduction of artificial pacemakers into clinical practice, many of the cardiac arrhythmias were either difficult to treat by other means or fatal.

Artificial cardiac pacemakers

Artificial pacemakers are small, battery-operated devices. At a basic level, all artificial pacemakers have a pulse generator, pacing leads and a basic programmer. The artificial pacemakers are of broadly three types: (a) external temporary pacemakers, (b) internal permanent pacemakers and (c) implantable cardioverter defibrillators.

The external pacemakers are commonly used as a temporary intervention before definitive procedures are done. They are small in size and typically about the size of a large mobile phone. The pulse generator and controls are placed externally well away from the heart and the electrodes are placed over the chest wall skin close to the heart. The external pacemakers can also be connected to a temporary pacing lead placed in the heart via a percutaneous intravascular route.

Implantable internal pacemakers are permanent cardiac pacemakers. They are very small in size, measuring less than 5.0 × 5.0 × 1.0 cm and weighing less than 40 g. They vary in sophistication ranging from simple single-chamber pacemakers to demand-mode dual-chamber pacemakers. These pacemakers typically have a life expectancy of 7–10 years. The usual position for the implantation of an internal cardiac pacemaker is a subcutaneous pocket over the pectoral muscles in the left infraclavicular region. They are inserted under the skin through a small incision, and the electrodes (‘pacemaker leads’) are threaded through veins into the heart without surgically opening the chest. The pacemaker leads (wires) lie in contact with cardiac musculature. The leads deliver electrical impulses to the heart and in most cases the leads sense the heart and carry signals back to the pacemaker generator. The modern pacemakers also have sophisticated programmable software and facilities for recording events.

Implantable cardioverter defibrillators (ICDs) are much more sophisticated devices and have entered widespread clinical practice over the past decade. ICDs have the ability to automatically defibrillate the heart. ICDs constantly monitor the heart rate and deliver appropriate electrical therapy (shock or over-drive pacing) in case of a serious arrhythmia being sensed by the pacemaker. ICDs have revolutionised the treatment of patients at risk of sudden cardiac death due to ventricular tachyarrhythmias. ICDs are light in weight and have a mini-computer powered by a lithium oxide battery, all sealed in a titanium case. They usually need to be replaced with in 4–8 years.

Traditionally, pacemakers have been widely used with a therapeutic intent in a wide range of cardiac arrhythmias. (e.g., complete heart block, sick sinus syndrome, atrial fibrillation, aberrant conduction disorders). Recently, there has been a surge of interest in prophylactic use of ICDs for patients at high risk of cardiac death. Cardiac resynchronisation therapy with biventricular pacing for heart failure is another growing application. Furthermore, pacemakers are also being used to prevent cardiac induced falls in elderly and treat sleep apnoea syndrome. Overall, the expanding indications are likely to increase the number of patients with artificial pacemakers in the general population.
Electromagnetic sources of interference in home and work environment

Electromagnetic interference can mimic normal cardiac activity as well as abnormal cardiac activity. Hence, any equipment with an electromagnetic source can potentially affect the functional and structural integrity of the pacemakers. Electromagnetic sources affect the pulse generator as well as the sensors of the pacemakers.

Many electromagnetic devices in the home and work environment have the potential to adversely interfere with pacemaker function. However, in practice, only a few adverse events have been reported. Common household devices such as electric blankets, electric toothbrushes, portable telephones, microwave ovens, portable audio devices, gaming consoles and personal computers have electromagnetic components but they can be safely used by patients with pacemakers.25

They have been a few reports of inappropriate shocks from electric razors because of the proximity to the electromagnetic field generated by the motors.26 Some devices like radio frequency remote controls may produce inappropriate sensing when held in close vicinity to the ICD device but they have not been shown to adversely affect pacemakers when the device is held >10 cm from the chest wall.27 Mobile phones can have a transient effect on pacemakers. But, if the phones are held more than 10 cm away from pacemakers for instance use of the contra lateral ear, they can be safely used.28

In the occupational environment, many devices have the potential to affect the functional integrity of the pacemakers. Heavy machinery and heavy-duty industrial motors can interfere with pacemaker function. Arc welding equipment and other devices that generate powerful magnetic fields are potentially unsafe in patients with implanted pacemakers. The anti-theft devices such as electronic article surveillance (EAS) systems have been shown to interfere with most cardiac pacemakers.29 Prolonged exposure of pacemaker to metal detectors may inactivate the pacemaker-programmed therapies. However, the metal detectors used in the airports usually do not cause pacemaker malfunction.30

Electromagnetic sources of interference in medical environment

Many electromagnetic sources found in the medical environment can cause transitory as well as permanent pacemaker dysfunction. The medical sources of electromagnetic interference (EMI) occur in two forms namely conducted EMI and radiated EMI. Conducted EMI can potentially occur when the electromagnetic source comes in direct contact with the body. Examples of conducted EMI include electrocautery and defibrillation.25 Radiated EMI can potentially occur when the body is placed within an electromagnetic field and unlike conducted EMI, no physical contact with the source is necessary. Examples of radiated EMI include magnetic resonance imaging (MRI), positron emission tomography (PET), lithotripsy and radiation therapy.25,31,32 Significantly no adverse effects have been noted with the use of diagnostic kilovoltage X-rays and CT-scanners.33

Pacemaker malfunction due to radiotherapy: mechanisms and consequences

The older generation of pacemakers, made up of bipolar semiconductor devices, are resistant to radiation damage at therapeutic doses of radiation. However, they are not in use any more and have now been completely replaced by programmable modern pacemakers. The modern pacemakers with complementary metal-oxide semi-conductor (CMOS) circuitry are more sensitive than the older devices. The pacemaker malfunction during radiotherapy is a consequence of radiation damage to hardware and software. Various mechanisms such as ionisation of semiconductor material, abnormal current flows, changes in threshold voltages and electrical interference from linear accelerator have been implicated.34 It is important to note that it is not only the pulse generators, which are affected; the sensors and conductors of the pacemakers could be affected as well. For instance alteration of stimulation threshold can occur due to thermal damage to electrode tips.12

The clinical consequences of electromagnetic interference could be transient such as dropped beats, transient inhibition or triggering of pacemakers. However, the consequences could be occasionally serious and permanent. For instance, severe circuitry damage can potentially lead to a major catastrophic failure of cardiac conduction system and ultimately death of the patient.

Early generation of pacemakers: in vitro and clinical data

Several in vitro studies have examined the effects of radiation on older generation of cardiac
pacemakers. As mentioned earlier, the older generation of pacemakers using the bipolar semiconductor technology appear to be resistant to therapeutic radiation and posed no problems during therapeutic radiation (Table 1).

Hildner et al.\(^{35}\) radiated two bipolar semiconductor pacemakers with a cobalt 60 unit. They irradiated a ventricular demand pacemaker with doses of up to 100 Gy in sequential 10 Gy fractions at a dose rate of 3 Gy per minute. They checked the performance of the pacemaker after each 10 Gy fraction. They irradiated a second pacemaker to a total dose of 460 Gy. They noticed no change in the output of the pacemakers either during or after the radiotherapy. A further performance check, 90 days after irradiation, again showed no compromise in the integrity of pacemaker function. Based on the in vitro evidence, Hildner et al. gave 35 Gy over 3 weeks to a patient with a right upper lobe tumor lying beneath a pacemaker. Similar to the in vitro setting, they noticed no change in the pacemaker function during or after radiotherapy.

Walz et al. also reported the radio resistant property of the older generation of pacemakers in 1975. Walz irradiated five models of demand type pacemakers with electron and photons.\(^{36}\) They utilised photon dose rates ranging from 0.5 to 10 Gy per min and electron dose rates ranging from 2 to 12 Gy per min. Even after a cumulative dose of more than 300 Gy, none of the pacemakers showed any signs of major malfunction. Minor transient effects (dropped beats) were noted when beam current was turned on and off. On one occasion, erratic pacemaker function was noted when the linear accelerator was in standby mode but this was not reproduced on repeat experiments. Like Hildner, they concluded that radiotherapy is not contraindicated in patients with pacemakers.

**Table 1** Early pacemakers

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Year</th>
<th>Diagnosis</th>
<th>Dose and outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hildner (35)</td>
<td>1969</td>
<td>Lung cancer</td>
<td>35 Gy/3 weeks: No change in pacemaker function on direct radiation</td>
</tr>
<tr>
<td>Hildner (35)</td>
<td>1969</td>
<td>2 × in vitro</td>
<td>100 Gy: No malfunction 460 Gy: No malfunction</td>
</tr>
<tr>
<td>Walz (36)</td>
<td>1975</td>
<td>In vitro; 5 models of demand pacemakers</td>
<td>No major effects on pacemaker function with photons and electrons doses up to 300 Gy Minor transient effects (dropped beats) were noted — when beam excitation circuit of the machine was turned on and off</td>
</tr>
</tbody>
</table>

**Modern pacemakers: in vitro studies**

Since the late 1970s, the CMOS circuitry has replaced the bipolar semi-conductors in the pacemakers. These modern pacemakers based on CMOS technology are very radiosensitive (Table 2). Marbach et al. were the first to raise concerns about modern pacemakers utilising CMOS circuitry. They irradiated four types of commercial pacemakers with six different types of modern machines producing photons and or electrons.\(^{11}\) To simulate a pacemaker implanted in a patient, they placed a pacemaker fastened to a Lucite block in a 0.2% saline bath maintained at a temperature of 31–37 °C. They monitored pacemaker function during and after irradiation. They reported that several pacemakers temporarily malfunctioned on exposure to radiation. They noticed permanent pacemaker damage only after a cumulative dose of between 70 and 120 Gy. They also noticed temporary failure of a pacemaker with 8 MeV linear accelerator beam even when the pacemaker was located outside the beam thereby indicating that the electromagnetic fields around a linear accelerator could be of sufficient magnitude to cause pacemaker malfunction. However, since their study in 1978, technological improvements have considerably constricted electromagnetic fields around a linear accelerator. Marbach et al. concluded that radiotherapy utilising linear accelerators is safe since the malfunctioning of the pacemaker was temporary. Moreover, since permanent pacemaker damage in their series occurred at doses higher than the commonly employed therapeutic doses, they concluded that monitoring of patients with an ECG during treatment is enough. Since, with one exception, all pacemakers failed with betatron, they recommended that betatron irradiation should be avoided in patients with pacemakers.
Contrary to the conclusion reached by Marbach et al., four years later Adamec et al. in 1982 recommended that irradiation of pacemakers should be avoided. Adamec et al. tested 12 ventricular demand pacemakers and 13 programmable pacemakers with radiation from a linear accelerator. They found the programmable pacemakers to be sensitive to radiation and 9 out of 13 pacemakers tested failed completely at doses ranging from 10 to 70 Gy. Even though the demand pacemakers were less radiosensitive, an alteration in functional integrity, which could be clinically significant, was noted. Based on this experimental evidence, they recommended that programmable pacemakers should not be directly exposed to therapeutic doses of radiation.  

Maxted in 1984 irradiated 19 pacemakers with 3 Gy fractions per day and noticed malfunction of hybrid pacemakers after a cumulative dose of 39–60 Gy. In addition, they noticed a reduction in radiation tolerance when the dose rate was increased. Venselaar et al. in 1985 irradiated six-demand type and two programmable pacemakers with a cobalt-60 beam. Two of the six-demand type pacemakers failed at cumulative doses of less than 100 Gy. The two programmable pacemakers failed at cumulative doses of 97 and 147 Gy, respectively. More importantly, they found electromagnetic interference from a linear accelerator when switching the machine on and off. Two years later, they published further data on 23 CMOS pacemakers, which were subjected to radiation in vitro. Five out of 23 failed at a dose less than 70 Gy. One pacemaker failed at a dose of 13 Gy. Like many other investigators, they also concluded that direct radiation of pacemakers is harmful and advised caution when treating patients with pacemakers. Rothig et al. also noted dose dependent failure of pacemakers and recommended removal of pacemakers after a cumulative dose of 5 Gy to pacemaker.

Rodriguez et al. irradiated 23 modern programmable pacemakers with CMOS technology and 4 implantable cardiac defibrillators with photon and electron irradiation at various doses. Eight out of 17 pacemakers showed signs of malfunction with photon doses of less than 50 Gy. Malfunction was noted even at doses as low as 14 Gy. They did not notice any significant difference in pacemaker radiation tolerance between electrons and photon irradiation. Four out of six pacemakers exposed

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Year</th>
<th>Pacemakers</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marbach (13)</td>
<td>1978</td>
<td>4 models of pacemaker</td>
<td>1 temporary failure due to electromagnetic disturbance from Linear accelerator. All models failed with Betatron radiation. With Linear accelerator, permanent dysfunction noted at doses &gt;70 Gy</td>
</tr>
<tr>
<td>Adamec (37)</td>
<td>1982</td>
<td>12 (VVI) 13 programmable</td>
<td>Mild changes in demand-mode pacemakers with doses ranging from 10 to 70 Gy: 9 of the programmable Sudden showed complete failure</td>
</tr>
<tr>
<td>Maxted (38)</td>
<td>1984</td>
<td>19</td>
<td>3 malfunctioned after doses 39–60 Gy</td>
</tr>
<tr>
<td>Venselaar (40)</td>
<td>1985</td>
<td>8 (Cobalt)</td>
<td>2 demand-mode pacemakers failed at doses &lt;100 Gy</td>
</tr>
<tr>
<td>Venselaar (39)</td>
<td>1987</td>
<td>22, 23</td>
<td>2 programmable pacemakers failed at 97 and 140 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 failed when LINAC switched on and off!</td>
</tr>
<tr>
<td>Venselaar (39)</td>
<td>1987</td>
<td>22, 23</td>
<td>&lt;13 Gy: 1 failed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;70 Gy: 5 failed</td>
</tr>
<tr>
<td>Rothig (41)</td>
<td>1990</td>
<td>Programmable pacemakers</td>
<td>Dose dependent failure (2 types of wiring diagram tested)</td>
</tr>
<tr>
<td>Rodriguez (43)</td>
<td>1991</td>
<td>23 pacemakers and 4 ICDs</td>
<td>8 of 17 pacemakers failed at Photons doses &lt; 50 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 of 6 pacemakers failed at electrons doses &lt;70 Gy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ICDs failed at 76 Gy</td>
</tr>
<tr>
<td>Anelli-monti (12)</td>
<td>1992</td>
<td>8 (cobalt)</td>
<td>10 Gy: minor changes</td>
</tr>
<tr>
<td>Ngu (46)</td>
<td>1993</td>
<td>4 Demand-mode (cobalt)</td>
<td>20–96 Gy: 6 malfunctioned</td>
</tr>
<tr>
<td>Wilm (44)</td>
<td>1994</td>
<td>20</td>
<td>70 Gy: No malfunction</td>
</tr>
<tr>
<td>Souliman (45)</td>
<td>1994</td>
<td>18 (3 dual and 15 single chamber)</td>
<td>All dual-chamber pacemakers malfunctioned at doses 16–64 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 of single-chamber pacemakers failed at doses 25–70 Gy</td>
</tr>
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</table>

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to electrons failed at a cumulative doses at less than 70 Gy. (1991). The ICDs using shorter channel length (3 μm CMOS) were found to be relatively radio resistant with failure occurring only at doses above 76 Gy.43

Anelli-monti et al. observed changes in pacemaker output with doses as low as 10 Gy. They found a wide range of radiation doses at which the programmability of pacemaker was lost.12 Wilm et al. irradiated 20 pacemakers and noted one pacemaker failure at 40 Gy and 19 failures at doses ranging from 90 to 300 Gy. They noticed minor perturbations even at doses as low as 10 Gy.44 Souliman et al. noticed a range of doses at which pacemakers malfunctioned. They irradiated 18 multi-programmable pacemakers and three pacemakers failed at doses less than 28 Gy and eight failed at doses less than 70 Gy.45 They concluded that pacemakers could temporarily or permanently fail at doses commonly used in the radiotherapy treatment. By contrast, Ngu et al. observed no effect on pacemaker function with doses as high as 70 Gy.46 One possible reason for their finding is that they employed less stringent testing methods.12

Last in 1998 recommended that the total dose to pacemakers should be less than 10 Gy and ideally should be less than 2 Gy based on many of the above-mentioned studies. The AAPM report by Marbach et al. also recommended that the maximum dose to pacemaker should be limited to less than 2 Gy. The AAPM report did not make any recommendations about dose rates partly because of paucity of data.13

A recent study from France, however, questions the validity of these recommendations. This large in vitro study, by Mouton et al., provides more valuable data regarding the radiation tolerance of modern multi-programmable pacemakers.14 Mouton et al. irradiated 96 pacemakers of different models at the Institute Gustav Roussy in Paris. They chose pacemakers of different ages and irradiated pacemakers not only with different doses but also with different dose rates. The pacemakers were irradiated in a water equivalent phantom with a high-energy linear accelerator (18 MeV). A range of dose levels up to 200 Gy and a range of dose rates from 0.05 to 8.0 Gy per minute were employed in their experimental setting. Like many other previous in vitro studies, they found the modern pacemakers to be very radiosensitive. However, unlike previous studies which defined the maximum tolerance dose to be as high as 5–10 Gy, they found the pacemakers to be much more radiosensitive. They found that the maximum radiation tolerance dose of 2–5 Gy quoted by the manufacturers’ is not reliable in all situations. They observed high radiation tolerance by some pacemakers (up to 140 Gy) but on the other hand, some pacemakers failed at very low doses. For instance, one of the irradiated pacemakers exhibited clinically significant disturbances at a cumulative dose of only 0.15 Gy. Two other pacemakers exhibited defects at a dose of 1 Gy and nine pacemakers failed at a cumulative dose of 2 Gy. A further 13 pacemakers failed at a cumulative dose of only 5 Gy. This has important implications for clinical practice. The majority of cancer patients, even when treated by palliative radiation, receive at least a total dose of 8 Gy. Given that pacemakers have the potential to fail even at this low cumulative dose, a significant clinical risk exists when irradiating most patients with cardiac pacemakers.14

Mouton et al. also found that pacemaker radiation tolerance was dose rate dependent for dose rates in clinically relevant ranges. The risk of pacemaker failure was high at dose rates of 8 Gy per minute and low at dose rates less than 0.2 Gy per minute. They concluded that the recommendations from the manufactures about maximum tolerable cumulative radiation doses are unreliable.

Modern pacemakers: clinical data

In spite of the potential hazards associated with irradiation of patients with pacemakers, there have been no prospective or retrospective studies evaluating the safety of radiotherapy delivery to cancer patients with pacemakers. The published evidence in the literature is mainly in the form of single case reports and almost all reports are of immediate malfunction. There are also scant data regarding the late manifestation of pacemaker malfunction induced by radiation. In spite of the paucity of large clinical studies, the available case reports reinforce the fact that the irradiation of pacemakers, even with palliative doses, poses a significant clinical hazard (Table 3).

Katzenberg were the first to report, in 1982, a clinical case of pacemaker failure after exposure of the circuitry to radiation. They reported the increased radiosensitivity of the newer generation of CMOS pacemakers to radiation. They gave post operative irradiation to a patient with right-sided breast cancer. The pacemaker was within one of the radiation portals and after a cumulative dose of 30–36 Gy, pacemaker malfunction was noted. An ECG showed a heart rate of 300 per min and the pacemaker was immediately replaced. Analysis of the removed pacemaker showed damage to the integrated circuit.47
Subsequently many others reported pacemaker failures following therapeutic radiation. \cite{48-50} Pourhamidi et al. irradiated a patient with squamous cell cancer of the thoracic oesophagus using 4 MeV photons and delivered 63 Gy in 35 fractions to the tumor. The pacemaker with CMOS circuitry was not in the centre of the field and the pacemaker was estimated to have received only 15 Gy in total. But unexpectedly even at this relatively dose permanent pacemaker circuitry damage was noted.\cite{48} Quertermous et al. initially gave 50.8 Gy in 27 fractions to a patient with right-sided lung cancer and right supra-clavicular nodal metastasis using photons from a linear accelerator. The pacemaker was not in the radiation portal during this treatment and the estimated scatter dose to the pacemaker was only 1.25 Gy. On a subsequent occasion, the patient needed right axillary irradiation. The patient became haemodynamically unstable after receiving 20 Gy in 10 fractions over 2 weeks. An ECG revealed a chaotic rhythm and the pacemaker was exchanged. A detailed examination of the pacemaker by the manufacturer revealed radiation damage to the metal-oxide circuitry.\cite{49} Lewin et al. irradiated the right axilla of a patient with haemangiopericytoma. Using parallel-opposed fields, they delivered 19.8 Gy in 11 fractions using a 6 MeV linear accelerator. After the 11th fraction, the patient was found to be tachycardic and the pacemaker had to be exchanged. A detailed laboratory examination confirmed radiation induced pacemaker failure.\cite{50} In all of the above case reports, the therapy was delivered by a fractionated regimen and significantly, all the failed pacemakers employed the CMOS technology.

Over the past two decades, there have been many other case reports of radiation induced pacemaker malfunction. In these case reports, similar to the above-mentioned case reports, the pacemakers failed with radiation doses less than 40 Gy. Lee et al. irradiated a patient with metastatic uterine cancer and delivered 39.6 Gy in 22 fractions to the para-aortic nodes. The pacemaker was outside the radiation field but was lying adjacent to the field edges. A week after completion of radiotherapy the patient was admitted with an ‘Atrial runaway’ rhythm and a heart rate of 300 beats per min. The pacemaker was replaced and an analysis of the pacemaker by the manufacturer showed circuitry damage consistent with radiation induced damage.\cite{51} Brooks et al. noticed pacemaker malfunction in an inoperable lung cancer patient treated with a palliative course of radiotherapy using a Cobalt-60 machine. The patient received a cumulative dose of 35 Gy and the malfunction manifested as pacemaker induced tachycardia several weeks later.\cite{52}

Pacemakers can be damaged not only by photon radiation but also by betatron and neutron therapy. Jaeger et al. irradiated a breast cancer patient initially with photons from a linear accelerator and then with betatron. Even though the pacemaker was well outside the radiotherapy fields, the pacemaker malfunctioned. This case again illustrates the extreme sensitivity of pacemaker to betatron therapy, which was previously noted in vitro by Marbach et al.\cite{53} Similarly, Raitt et al. noticed pacemaker malfunction in the form of tachycardia with a dose of only 0.9 Gy in a patient having neutron beam radiotherapy for thyroid cancer. Evaluation of the pacemaker by the manufacturer revealed signification alteration in the programming code of the

<table>
<thead>
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<th>Table 3</th>
<th>Modern pacemakers: case reports</th>
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<tbody>
<tr>
<td>Author (Ref.)</td>
<td>Year</td>
</tr>
<tr>
<td>Katzenberg (47)</td>
<td>1982</td>
</tr>
<tr>
<td>Pourhamidi (48)</td>
<td>1983</td>
</tr>
<tr>
<td>Quertermous (49)</td>
<td>1983</td>
</tr>
<tr>
<td>Lewin (50)</td>
<td>1984</td>
</tr>
<tr>
<td>Lee (51)</td>
<td>1986</td>
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<tr>
<td>Nibhanupudy (56)</td>
<td>2001</td>
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pacemaker microprocessor. This case illustrates the extreme sensitivity of pacemakers to neutron beam radiation.

In contrast to the above-mentioned case reports, recently there has been case reports of safe radiotherapy delivery to patients with pacemakers. Mueller-Runkel et al. treated a patient with inoperable left lung cancer with radical RT. The patient received a cumulative dose of 64 Gy to the tumour and a Cerrobend block mounted on a tray shielded the pacemaker implanted on the left side. Using a TLD, they estimated the scattered dose received by the multiprogrammable CMOS pacemaker. The patient was monitored during and after radiotherapy. They were unable to detect any malfunction of the pacemaker which received an estimated cumulative dose of 6.2 Gy. Ngu et al. irradiated a patient with a CMOS pacemaker and found no pacemaker malfunction with a cumulative dose of 0.55 Gy to the pacemaker from a cobalt-60 beam. Nibhanupudy et al. used 6MV X-rays to treat a patient with left breast cancer. The patient had a pacemaker implanted on the left chest wall and the pacemaker was removed before radiotherapy and reimplanted 4 cm away from the radiation field. Using three types of measuring devices (silicon diode, farmer chamber and lithium fluoride TLD) they measured the dose to the pacemaker in the patient. The pacemaker received a cumulative dose of 1.6–1.8 Gy without any interference in its function. Similarly, Ngano et al. successfully treated a patient with cardiac lymphoma with chemotherapy and radiotherapy. Niehaus et al. irradiated three patients with ICDs and at a cumulative dose of less than 5 Gy, no pacemaker malfunction was noted. Our group irradiated six patients with implanted pacemakers during a 4-month period and no pacemaker malfunction was noted. The calculated dose to the pacemaker ranged from 0.5 to 1.3 Gy in five patients. In an elderly patient with breast cancer, the pacemaker was directly in the radiation field and received 26.7 Gy in 10 fractions. Clinically, the patient did not have any signs of pacemaker malfunction. These case reports illustrate the fact the radiotherapy could be successfully delivered to patients with pacemakers if adequate precautions are taken.

**Technological strategies to protect pacemaker**

Most of the living and working environment is full of various devices that can cause electromagnetic interference. Hence, various technical improvements have been made in pacemaker design to minimise the impact of electromagnetic interference in the home and medical environment. These technological improvements have increased the ability of a pacemaker to discriminate between electromagnetic interference and cardiac signals. The protective measures include the introduction of an anti-interference circuit and sensitivity filters, as well as the use of bipolar electrodes, titanium casing and asynchronous stimulation. Other measures include incorporation of a band pass filter, which prohibits the entry of signals that are above or below a certain frequency threshold and the introduction of Zener diodes, which are designed to shunt high levels of current flow away from the delicate internal circuitry. A detailed description of the technological strategies to protect the pacemakers is beyond the scope of this review.

**Conclusion**

Modern multi-programmable pacemakers are very sensitive to therapeutic megavoltage irradiation. There is no safe radiation threshold for megavoltage radiation. Even when the pacemaker is not in a radiation field, scatter radiation has the potential to cause pacemaker malfunction. However, radiotherapy is not absolutely contraindicated in cancer patients with artificial pacemakers. Radiotherapy can be safely delivered if direct irradiation of pacemakers is avoided, adequate monitoring is done during irradiation, and the dose to the pacemaker generator is kept below 2 Gy. Close liaison with the cardiologist and a pacemaker clinic; close monitoring of patients during the course of the treatment and for a few weeks thereafter and re-evaluation of pacing and sensing function after radiotherapy is essential.

From a clinical governance point of view, there is an urgent need to put a clinical risk management strategy in place to prevent life threatening complications. Failure to identify patients with cardiac pacemakers before irradiating them is perhaps the most important risk factor. There will be an increasing number of cancer patients with pacemakers in future and irradiation of the patients needs to be done safely. Radiotherapy departments should have protocols in place to identify and care for cancer patients with pacemakers. The recommendations in this review article should help radiotherapists to safely plan and deliver radiotherapy to patients with pacemakers.

Patient education has an important role too, and all patients with pacemakers need to be made aware of the risk of pacemaker malfunction with
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radiotherapy. There is also a need for prospective cohort studies to assess the short and long term effect of radiation on the functional integrity of pacemakers. This needs to be accorded a high priority by large cooperative oncology groups since with the inevitable ageing of the population and expanding indications for pacemaker implantation, a considerable proportion of cancer patients will have pacemakers in the future.

Clinical strategies to protect a pacemaker and recommendations

Based on the literature review, we recommend that the radiotherapy departments take the following measures to minimise the risk of pacemaker malfunction during delivery of radiotherapy to patients with artificial pacemakers. These recommendations are to be used as a general guideline only and each patient needs to have individualised care in consultation with the relevant cardiologist and a pacemaker clinic.

1. Adequate cardiac history should be obtained from all patients due to have palliative and radical radiotherapy. This will help to identify patients with cardiac pacemakers and this simple procedure already works very well in the MR Imaging facilities. A full assessment of patients with a pacemaker is mandatory.

2. Close liaison with the cardiologist and the pacemaker clinic is essential before, during and after treatment. The indications for pacemaker insertion, the extent to which the patient is dependent on the pacemaker and the potential complications that might occur should the pacemaker fail in any given patient should be ascertained with the cardiologist.

3. The make and model of the pacemaker, and the manufacturers’ recommendations regarding safe doses for that particular model of pacemaker should be ascertained. The manufacturer should also be asked to provide radiation tolerance information regarding relative sensitivity of the pacemaker to previous models. It has to be noted that not all data would be in the public domain and technological improvements occur all the time and radiation tolerance data pertaining to a particular model are essential.

4. The functional integrity of the pacemaker at the most recent visit to the pacemaker clinic should be ascertained.

5. A baseline electrocardiogram (ECG) should be obtained in all patients with pacemakers. This will help with assessment of pacemaker dependency. However, formal interrogation in a pacemaker clinic may also be required and is probably desirable before commencing radiotherapy.

6. The low energy, kilovoltage X-rays used in simulation for radiotherapy planning and CT scanners are unlikely to cause malfunction of pacemakers.33

7. The authors suggest categorising the patient into three risk groups based on potential clinical risks. (Low, Medium and High risk groups). Low risk patients are those who are not pacemaker dependent, the pacemaker is not directly in the radiation field and the dose to the pacemaker is likely to be less than 2 Gy of scattered radiation. Medium risk patients are those who are pacemaker dependent, the pacemaker is not directly in the radiation field, and the dose to the pacemaker is likely to be less than 2 Gy of scattered radiation. High-risk patients are those who are pacemaker dependent, the pacemaker is not directly in the radiation field and the dose to the pacemaker is likely to be more than 2 Gy of scattered radiation. Patients with pacemakers directly in the radiation field fall into a high-risk category irrespective of the total radiation dose. Direct radiation of pacemakers at therapeutic levels should be strictly avoided in a pacemaker dependent patient unless a backup system is in place. It has to be noted that the ‘radiation dose to a pacemaker’ is the ‘dose to any part of the device’ and is not the dose averaged over the volume of the device.

8. The majority of the patients encountered in the radiotherapy department do not have a pacemaker directly in the beam and therefore a radical change to the prescribed treatment is usually not necessary. Simple changes in the treatment plan may reduce the dose to the pacemaker to a low risk level.

9. For medium and high-risk patients, alternative treatment modalities such as surgery, hormone therapy or chemotherapy should be pursued if they are equally valid treatment options and appropriate for that patient.

10. If radiation is necessary for a medium or high risk patient, consideration should be given to surgically shifting the pacemaker to a region of less radiation dose.36,60
11. From a practical viewpoint, when dealing with any patient with an implanted pacemaker, the main priority is to keep the radiation to the pacemaker as low as possible. This could be done by various ways. For instance, the pacemaker could be excluded from radiotherapy portals by choosing appropriate gantry angles and field positions. By using MLCs and wedges, pacemaker exposure to scatter radiation could be minimised. If, despite best efforts, the pacemaker is near a radiation portal, the pacemaker could be shielded with lead alloys of appropriate thickness. By selecting appropriate radiation quality, energy and modality, pacemaker exposure to radiation could be minimised. For example, electrons could be used to treat a lesion near the posterior part of the thoracic wall instead of the photons and this would minimise pacemaker exposure to the exit dose at the anterior chest wall.

12. The use of high precision dose delivery techniques such as IMRT and stereotactic treatment may be of potential benefit in relation to reducing the dose to a pacemaker. The pacemaker could be considered like an ‘organ at risk’ with the usual planning considerations.

13. In pacemaker dependent patients, where the pacemaker would receive a significant dose, one option is to irradiate with a backup temporary external pacemaker, which is kept well away from the radiation field.

14. In patients who are not pacemaker dependent, if the pacemaker irradiation could not be avoided, the pacemaker could be sacrificed after consultation with the cardiologist and the pacemaker could be replaced after the completion of radiotherapy.

15. During irradiation of low risk patients, a baseline ECG and subsequently, weekly ECGs should suffice. Patients should be advised to report any signs of palpitations, dizziness, shortness of breath or any other cardio-respiratory symptoms during or after radiotherapy.

16. During irradiation of high and medium risk patients, personnel trained in advanced cardiac life support should be available. The cardiac arrest trolley should be periodically checked and replenished. Ideally, high risk patients should be irradiated in a hospital setting where there is an on call cardiac arrest team.

17. During irradiation of medium risk patients, a baseline ECG and subsequently, daily ECGs are necessary. In addition, patients should have their pulse and blood pressure checked after each radiotherapy fraction and patients should be actively questioned about cardio-respiratory symptoms each day.

18. During irradiation of high-risk patients, in addition to procedures mentioned for medium risk patients, some form of active monitoring should be done during radiotherapy. This might entail utilisation of cardiac monitors, which are viewed through using close circuit television. It has to be borne in mind that even the cardiac monitors themselves could be affected by linear accelerators and radiation. Hence, if cardiac monitors are used, they should be placed outside the linear accelerator room using long leads. In addition, pacemaker function should be checked by the pacemaker clinic each week.

19. It is essential either to measure or calculate the dose of radiation received by the pacemaker. The total dose to the pacemaker can be estimated by diode, ionisation chamber or by TLD measurements. In practice, it is difficult to make precise measurements using these methods even if the treatment is reproduced in a phantom. Moreover, the accuracy of measurements at the field edges and measurement of scattered dose at the surface might be doubtful. Calculation of dose, on the other hand, may provide estimates that are more accurate especially, when assisted by virtual simulation.

20. Following the completion of radiotherapy, all patients should be followed by the pacemaker clinic. The cardiologist should be informed about the completion of radiotherapy and the dose received by the pacemaker. If there are any signs of radiotherapy damage, the pacemaker should be immediately exchanged.

21. All the staff in radiotherapy department should be educated about the potential risks involved in irradiating a patient with pacemaker.

22. The patients should also be educated about the risks of late malfunction of pacemakers due to latent radiation damage so that they can seek immediate medical attention in case of an emergency.

References

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