Using honey to treat skin damaged by radiotherapy

About 95% of people who have radiotherapy have an adverse reaction in the surrounding tissues. Non-healing ulcers may develop at any time following radiotherapy — even decades after. There is little evidence to support the use of any interventions or products for the care and treatment of radiotherapy skin reactions. However, it has been shown that honey may be useful as a topical antimicrobial for radiotherapy-damaged skin. It may also be able to interrupt the early damaging effects of radiation on cutaneous tissue. This article looks at the nature of radiotherapy damage and the evidence behind treatment methods.

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KEY WORDS
Honey
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Radiotherapy is a major modality in the treatment of cancer. More than 50% of all cancer patients receive some form of radiotherapy for tumour control pre- or post-operatively (Bentzen and Overgaard, 1994; Holmes, 1988; Mendelsohn et al, 2002). Even though radiotherapy is targeted at a particular location and depth, tissues overlying the site can also be affected and may react to the treatment, this happens in about 95% of patients (De Conno et al, 1991; Porock and Kristjanson, 1999).

Over the past 30 years the International Agency for Research on Cancer (IARC) has prepared estimates of the global cancer burden. This estimate included 10.9 million new cases of cancer globally for 2002 (Parkin et al, 2005). The most recent incidence and mortality data on which these estimates have been based are from the period between 1993 and 2001. It is estimated that in England and Wales one in three people will develop cancer during their lifetime. In 2005, 239,000 new cases of malignant cancer (excluding non-melanoma skin cancer) were registered (National Statistics, www.statistics.gov.uk). In Scotland 36,509 new cases were registered in 2005 (NHS Scotland, National Services Scotland, www.isdscotland.org). Each year the American Cancer Society (ACS) estimates the number of new cancer cases expected in the USA and for 2007, based on incidence data through to 2003 and mortality data through to 2004, a projected total of 1,444,920 new cases were anticipated (Jemel et al, 2007).

Survival rate for cancer was estimated globally in 2002 as 24.6 million alive with cancer within three years of diagnosis (Parkin et al, 2005). Cancer survival in England and Wales for 1996–1999 (for all cancers combined) confirm that the five-year relative survival rate has now reached 50% (Office for National Statistics, 2003). In Scotland, the five-year relative survival, taking all cancers combined, for the period 2000–2004 is 42% for males and 51% for females (NHS Scotland, National Services Scotland). From the National Cancer Institute, USA, Surveillance Epidemiology and End Results (SEER) data for 1996–2004 in the USA, 65.3% of people were five-year survivors (www.seer.cancer.gov). Although geographical, race, age and sex variations exist, it is a fair estimate that half the long-term survivors will have had radiotherapy as a primary treatment or in combination with surgery and/or chemotherapy (Bentzen and Overgaard, 1994). Delaney et al (2005) pointed out that 52% of cancer patients are expected to receive radiotherapy and estimated that for 40% of those patients surviving at least five years, radiotherapy had contributed either alone, or in combination with other treatments and surgery, to their survival.

Radiation damage

Radiation tissue damage or injury refers to the morphological and functional changes that occur in non-cancerous tissue as a direct result of ionising radiation (Mendelsohn et al, 2002). Radiotherapy induces the formation of free radicals and peroxides which effect adverse changes in DNA, proteins and cellular membranes. Although cells have scavenging mechanisms to remove these dangerous free radicals, repeated bouts of radiation overwhelm them. DNA may be affected by breaks in either single or double strands, and cross-linking between strands may develop. Repair enzymes normally operate to remove these changes. If the

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damage is extensive, repair may not be successfully completed and cells die by apoptosis. If repair is effected, normal cell function is retrieved, but incomplete restoration leads to permanent changes (or mutations) that give rise to dysfunctional cells. The acute side-effects are greatest in cells that are actively dividing such as skin, bone marrow and gastrointestinal mucosa (Porock and Kristjanson, 1999). Severity of the adverse effects of radiation is dependent upon the radiosensitivity of the body sites being treated, the total dose and the rate of accumulation of cellular defects (Porock, 2002; Denham and Hauer-Jensen, 2002; Stone et al, 2003).

There are parts of skin that have an elevated risk of damage, such as where two skin surfaces are in contact (e.g. breast, perineum), or areas where the epidermis is thin and smooth (e.g. axillae, face, perineum), or sites where the skin integrity has already been damaged (e.g. from surgery, burns or lesions) (McQuestion, 2006). Comorbidities such as diabetes, renal failure, hypertension, age, compromised nutritional status, smoking, drug therapy, chemotherapy and skin colour may also affect the tissue reaction to radiotherapy. Furthermore, it is suggested that some patients may have a genetic susceptibility to developing radiation injury. Patients with ataxia telangiectasia develop severe reactions because of the defect in the repair of DNA after exposure to radiotherapy (Porock, 2002; Stone et al, 2003; McQuestion, 2006).

Response to radiotherapy

The normal response to traumatic injury involves a complex cascade of events involving:

- Haemostasis (immediate)
- Inflammation (day 0–4)
- Granulation tissue formation (day 3–3 weeks)
- Matrix deposition and remodelling (week 3–2 years)

(Denham and Hauer-Jensen, 2002; Dormand et al, 2005).

Many responses/effects following radiotherapy damage are similar to those following traumatic injury. However, the accumulating and repetitive damage during the course of treatment affects the 'normal' tissue that is within the radiation field. Thus, 'normal' tissue that was irradiated at the start of treatment is qualitatively very different to that same tissue when it is irradiated later (Denham and Hauer-Jensen, 2002).

Radiation injury is commonly classified as acute, late effects and consequential late effects according to the time before appearance of symptoms.

Acute effects

Radiotherapy leads to apoptotic cell death in malignant and healthy cells within the radiation field, as well as multiple cellular effects in surviving cells (Stone et al, 2003; Dormand et al, 2005; Maddocks-Jennings et al, 2005). The physical trauma results in the activation of an acute inflammatory response (Dormand et al, 2005). Although the changes that occur in the skin can start within hours of treatment, they may last for several months or even be permanent (Maddocks-Jennings et al, 2005). During the first two weeks of treatment the patient may experience soreness, erythema and/or burning, and the area may be sensitive and feel tight. If the total radiation dose to the skin does not exceed approximately 30 Gy (Gy, the measure of radiation dose), the erythema phase is followed during the fourth or fifth week by a dry desquamation phase, characterised by pruritus, scaling, and an increase in melanin pigmentation in the basal layer. Within two months, inflammatory exudate and oedema subside, leaving an area of pigmentation. If the total radiation dose to the skin is 40 Gy or greater, the erythema phase is followed by a 'moist' desquamation phase. This stage usually begins in the fourth week and is often accompanied by considerable discomfort. Bullous formation occurs, the rooves of the bullae are shed and the entire epidermis may be lost in portions of the irradiated area. Oedema and fibrinous exudate persist. In the absence of infection, re-epithelialisation usually begins within 10 days. Ulcers may appear at any time from approximately two weeks after radiation exposure. Ulcers formed in the early stage are a result of direct necrosis of the epidermis, these ulcers usually heal but tend to recur (Mendelsohn et al, 2002; Dormand et al, 2005; Maddocks-Jennings et al, 2005; McQuestion, 2006).

Late effects

Late effects develop months or years after treatment including necrosis, atrophy, fibrosis, vascular damage and carcinogenesis. Late effects tend to develop in tissues with a slow turnover of cells, such as subcutaneous tissue, fatty tissue, muscle, brain, kidney and liver (Stone et al, 2003). Non-healing ulcers may develop at any time following radiotherapy and up to decades afterwards (Dormand et al, 2005). A report has already been published of a case where the use of honey on a chronic wound that had developed on tissue damaged by radiotherapy 30 years earlier promoted successful healing (Robson et al, 2005).

Consequential late effects

In some patients acute reactions fail to heal completely. Consequential late effects are increasingly being observed because of the introduction of new aggressive treatment regimes with combined modalities, such as radiotherapy and chemotherapy (Stone et al, 2003).

Treatment options for radiation tissue damage

Currently, there is little objective evidence to support the use of any interventions or products that are currently available for the care and treatment of radiotherapy skin reactions. A survey that was completed in 1992 with information collected from 31 radiotherapy centres, hospices, and community and specialist nurses in the UK found that of the 112 individuals who responded, 69.6% had used creams or ointments on radiotherapy-damaged skin. From those practitioners, a total of 40 different topical products were identified. Comparatively fewer responses were received in relation to the use of dressings for the

management of radiation-damaged skin. Only 17 dressings were identified and when asked which dressings were thought to be unsuitable for this kind of wound care, 17 products were specified. Some of the dressings promoted by some respondents were considered unsuitable by others. The author of the survey inferred that the observations suggested either dissatisfaction with the dressings that were available or a failure to appreciate the advantages of newer dressings (Thomas, 1992).

At present, irradiated wounds are cared for in a similar manner to other chronic wounds because their exact microenvironment has not yet been fully characterised (Hom et al, 1999). Accurate holistic assessment of the wound is advised. Adequate debridement followed by a dressing that promotes granulation tissue formation has been recommended; adhesive dressings are avoided to prevent epithelial injury (Hom et al, 1999). A recently published review of the literature recommends topical antimicrobial therapy with antiseptics to prevent infection in radiotherapy ulcers (Olascoaga et al, 2008).

There are numerous small studies making various recommendations such as hydrocolloid dressings (Margolin et al, 1990; Mak et al, 2000), topical negative pressure (TNP) (Schimp et al, 2004), hyperbaric oxygen (Borg et al, 2001), and Mepilex® Lite soft silicone dressing (Mölnlycke Health Care, Göteburg) (MacBride et al, 2008). A study in the Netherlands on 24 patients who suffered skin reactions from radiotherapy were randomised into two groups. The control group received a paraffin gauze dressing and the study group had honey-impregnated gauze applied. Although no statistical significance was found, the authors concluded that the honey group displayed a trend towards faster healing of skin reactions and had greater patient satisfaction (Moolenaar et al, 2006).

Three clinical studies have advocated the use of honey in the management of radiation mucositis in patients with head and neck cancer receiving radiation to the oropharyngeal mucosal area. In one study, 40 patients were divided into two equal groups. The control group received radiotherapy alone and the study group received radiotherapy plus topical honey. A significant reduction in the symptomatic grade 3/4 mucositis was seen in honey-treated patients compared to the control group (Biswal et al, 2003). In a similar study of 40 patients, significantly reduced mucositis, as assessed by the Oral Mucositis Assessment Scale (OMAS), in the honey-treated patients was reported. Compared with a normal saline rinse, honey before and after radiotherapy was found to give statistically significant reduction in OMAS throughout a six-week treatment period (Motallebnejad et al, 2008). In a third study on head and neck cancer patients, 40 patients were randomised to receive honey or no treatment as a prophylactic measure. Oral and pharyngeal mucositis were assessed and, oropharyngeal swabs were cultured for aerobic bacteria and Candida spp. In the honey-treated group, fewer patients developed mucositis ($p<0.05$) and fewer positive cultures for either Candida spp. ($p=0.003$) or aerobes ($p=0.007$) were reported, compared with the untreated group (Rashad et al, 2008).

Honey seems to offer potential in the treatment of radiation-damaged tissue in several ways. It is a broad spectrum antimicrobial agent that has the potential not only to prevent infection, but also to eradicate bacteria from wounds (Cooper, 2008). Since infection is a possible complication in such tissue (Hom et al, 1999), the antimicrobial properties of honey may be advantageous. Honey has also been shown to contain components that quench free radicals and act as anti-inflammatory agents (Henriques et al, 2006; Beretta et al, 2007; van den Berg et al, 2008), and, therefore, it may be able to interrupt the early damaging effects of radiation on cutaneous tissue.

Conclusion

Skin reactions and delayed post-operative wound healing is common in patients during radiotherapy and in those who have received treatment in the past (De Conno et al, 1991; Porock et al, 1999; MacBride et al, 2008). Although many different treatments have been suggested for the management of these wounds and the importance of selecting suitable dressings and topical treatments is recognised, there appears to be a lack of robust evidence to support any one treatment and variability remains within practice. Such wounds are often resistant to conventional therapy and pose a major problem as they may result in chronic ulceration and infection, heavily impacting on the patient's health and quality of life as well as draining economic resources. The lack of an assessment tool to evaluate irradiated skin reactions is an obstacle to the formulation of suitable clinical guidelines and helps to explain why none have yet been developed (Nystedt et al, 2005). Skin cleanliness, adequate hydration and the use of moist healing principles seem appropriate (Porock et al 1999; Wickline 2004; Nystedt et al, 2005). Several trials have evaluated various topical treatments and have raised the uncertainty of any treatment being effective in this area of care. This indicates that further research is warranted. Honey has not been subject to objective clinical evaluation in this field but the growing evidence for its use in chronic wound care merits its consideration in this demanding area. In Liverpool, honey is becoming increasingly popular in the management of ENT patients (Robson et al, 2007), and effective outcomes in managing radiation-damaged skin are beginning to be reported (Robson and Cooper, 2009). WUK

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Key Points

- About 95% of patients who have radiotherapy have an adverse reaction in the surrounding tissues
- Severity of the adverse effects of radiation is dependent upon the radiosensitivity of the body sites being treated, the total dose and the rate of accumulation of cellular defects.
- Such wounds are often resistant to conventional therapy and pose a major problem as they may result in chronic ulceration and infection, heavily impacting on the patient's health and quality of life
- Honey seems to offer potential in the treatment of radiation-damaged tissue in several ways. It may be able to interrupt the early damaging effects of radiation on cutaneous tissue..