Medical Xpress

Stem cell sparing radiotherapy for head and neck cancer may avoid salivary gland damage

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Barcelona, Spain: Researchers believe they may have found a way to avoid damaging salivary glands during radiotherapy treatment for head and neck cancer – a discovery that could improve the quality of life of 500,000 patients a year worldwide with the disease.

Presenting their findings to the 31st conference of the European Society for Radiotherapy and Oncology (ESTRO31), the researchers said that they had discovered that the stem cells essential for regenerating the parotid gland (the largest pair of salivary glands) were located mainly in its major ducts, and that these could easily be avoided during radiotherapy or given a minimal radiation dose. "This would significantly reduce complications arising from radiotherapy for head and neck cancer," said Dr Peter van Luijk, a research associate at the University Medical Center Groningen, The Netherlands.

Around 40% of patients treated for head and neck cancer suffer from the distressing side-effects of dry mouth syndrome – a condition that can occur when the parotid gland stops working properly after radiation damage. This causes problems with eating, sleeping, speech, tooth loss and oral hygiene, leading to diminished quality of life, social isolation and difficulty in continuing work. Attempts to treat dry mouth syndrome and its consequences can cost hundreds or even thousands of Euros per patient per year and are mostly insufficient.

Dr van Luijk said: "Parotid gland dysfunction after radiotherapy for head and neck cancer was, and still is, a major clinical problem. During

radiotherapy, attempts to minimise the risk of this complication have been aimed at reducing the average dose to the salivary gland, on the assumption that it would not make a difference where in the gland the radiation dose was reduced. However, this does not seem logical according to the anatomy of the salivary gland and, in previous work, we discovered that reductions in the radiotherapy dose to some parts of the gland allowed the parotid gland to regenerate, whereas a dose to other parts did not. Therefore, we decided to investigate the reason for these regional differences. We hypothesised that our observations could be explained by a non-uniform distribution of stem cells necessary for the long-term maintenance of organ function and affected by irradiation."

Dr van Luijk and his colleagues investigated the location of stem cells and the effects of radiotherapy to particular regions of the gland first in mouse and rat models, and then in parotid and salivary gland tissue taken from patients (after informed consent) undergoing a neck dissection for head and neck cancer.

They found that in mouse, rat and human tissue, the stem cells were predominately located in the major ducts of the parotid gland. "We have found in previous work that these stem cells are capable of regenerating a parotid gland when they have been transplanted after irradiation," said Dr van Luijk.

Dissection of the rat parotid gland and culturing of the different parts of the gland in Petri dishes showed that a greater concentration of stem cells capable of regenerating the gland were located in the centre, where the largest ducts are located. The researchers then directed high-precision irradiation at this centre part in living rats and found that it resulted in excessive reduction of saliva production, in contrast to the minimal effects observed after irradiating other parts of the gland.

Dr van Luijk explained: "The position of the stem cells in rats

corresponds to the cranio-ventral extension of the gland in humans, where the excretory duct leaves the gland on the ventral, or outward-facing side. So even though the glands have different shapes in rats and humans, the stem cells are in the exact same anatomical structure."

The researchers then tested their hypothesis by creating a mathematical model based on the treatment of 36 patients, which enabled them to estimate the expected parotid gland function depending on the dose to the stem cells.

"Excitingly, dose to the cranio-ventral extension of the gland containing the major ducts was most predictive of damage to saliva production. In addition, we found that it was possible to reduce the dose by approximately 50% to this part of the gland, without increasing the average dose to the whole gland or the dose to other critical structures in the head and neck region, and without compromising adequate target coverage," said Dr Van Luijk. "Using the mathematical model, we estimated that with such dose reduction none of the patients would have developed parotid gland dysfunction. This is, however, a hypothesis that needs to be tested prospectively in a randomised clinical trial by comparing parotid gland function in a group of patients treated with current standard to a group in which, additionally, the dose to the stem cells is minimised using our proposed stem cell sparing technique. This technique should only be implemented in radiotherapy clinics when such a trial proves there is a benefit as predicted by our research."

He continued: "Our findings can be seen as a proof-of-principle that elucidation of biological mechanisms in complications may lead to the identification of critical sub-structures of organs, possibly leading to new opportunities to reduce harm to normal tissue. Though we only show this for the parotid gland, such approach may apply to other organs as well."

The researchers say that it is easy to spare the parotid gland during

radiotherapy. "The stem cell region is on the side of the gland that is normally furthest away from the target area containing the tumour cells. Since only this area needs a high radiation dose, this distance makes avoiding the stem cell area easier than avoiding other parts of the gland," said Dr van Luijk.

"Based on our results we hypothesise that sparing the parotid gland stem cell region, costing around €100 in extra man-hours, may effectively prevent salivary gland dysfunction. This will allow patients to more readily lead their normal lives without having to rely upon medical care and welfare. Maybe even more importantly, cancer patients will remain productive members of society, realising a cost reduction far beyond the cost of medication. Finally, it will improve quality of life of 500,000 patients treated with radiotherapy for head and neck cancer worldwide every year," he concluded.

Professor Bradly G. Wouters (PhD), a radiobiologist at the Ontario Cancer Institute, Princess Margaret Hospital, Toronto, Canada, and chair of the conference radiobiology track, commented: "This is an exciting clinical study that has identified a critical region of the salivary gland that contains stem cells that can regenerate the gland and preserve function in patients with head and neck cancer. Using advanced radiation techniques the investigators show it is possible to spare this region and thus deliver higher therapeutic doses without causing more toxicity to patients."

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