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Clinical Oncology
The Royal College of Radiologists

Incidental irradiation of the spleen
RCR guidance

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Contents

Foreword

The spleen is seldom irradiated intentionally and is rarely considered an organ at risk (OAR) in other treatments. While computed tomography (CT)-planned radiotherapy enables treatment to be much more accurate, it can also highlight unforseen risks to normal tissues. As the authors of this guideline explain, irradiating tumours in the lower lung or upper abdomen can result in clinically significant doses of unwanted splenic radiation. Radiotherapy teams need to contour the spleen as an OAR and to develop protocols for vaccination and antibiotic prophylaxis if the mean dose exceeds 10 Gray (Gy).

Many thanks go to the team at University College London Hospital (UCLH) for highlighting this issue and to Tom Richards, Beatrice Seddon, Mark Gaze and colleagues for leading the development of this guidance.

This document is based on the UCLH Radiotherapy Department Guideline: *Radiotherapy to the spleen (as an organ at risk)* which has been adapted for national use.

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1. Introduction

The purpose of this guidance is to raise awareness of the spleen as an organ at risk (OAR) structure and to ensure that, for all patients receiving radiotherapy to the spleen, the risk of resultant functional hyposplenism is assessed and decisions on appropriate management are made if required.

The guidance applies to all patients who may receive radiotherapy to the spleen as a defined OAR as a result of being referred for radiotherapy to the upper abdomen or an adjacent anatomical site where the upper abdomen might also be irradiated. Treatment may be delivered using photon or proton external-beam radiotherapy to a range of tumour sites.

2. Background

Historically, the potential risks of radiotherapy to the spleen have not been well recognised among clinicians treating adult patients. A recent publication has highlighted a similarly low level of awareness among clinicians treating paediatric patients.[1]

Patients who have an absent or dysfunctional spleen are at risk of overwhelming sepsis from encapsulated bacteria, which can be potentially fatal (overwhelming post-splenectomy infection, OPSI). OPSI is a medical emergency; it has a mortality rate of 50–70%, with most deaths occurring in the first 24 hours. The risk of OPSI is 0.23–0.42% per year, with a lifetime risk of 5%.[2–4]

The spleen is recognised to be very radiosensitive and radiotherapy can impact on splenic function. A study of 20,026 survivors of childhood cancer – diagnosed aged ≤21 years – assessed the long-term impact of splenic radiotherapy (mean dose to the left upper quadrant of the abdomen reconstructed from previous radiotherapy planning details; no information was given on dose or fractionation schedules).[5] There were 62 deaths related to sepsis among the 20,026 survivors (the absolute number of events was very low). Splenic radiotherapy was associated with:

- Increased late infection-related mortality per 1,000 person years
- Increased cumulative incidence of late infection-related mortality at 35 years.

This appeared to be related to radiotherapy dose, with increasing risk relating to escalating dose. Even moderate radiotherapy doses (>10 Gy) were associated with increased risk.

	Late infection-related mortality (per 1,000 person years)	Cumulative incidence of late infection-related mortality at 35 years	Relative risk of infection-related mortality	
Splenectomy	0.67	1.5% (95% confidence interval (CI), 0.7% to 2.2%)	7.7	
Splenic radiotherapy	0.16	0.6% (95% CI, 0.4% to 0.8%)	0.1–9.9 Gy 10–19.9 Gy 20 Gy	2.0 5.5 6.0
Neither	0.05	0.2% (95% CI, 0.01% to 0.4%)		

A small retrospective single-institution study of 46 evaluable patients out of 90 consecutive patients receiving postoperative chemoradiotherapy (45 Gy in 1.8 Gy per fraction) for gastric cancer showed that 46% of patients received ≥20 Gy to the spleen, with a median D_{mean} of 40 Gy.[6] The splenic volume was assessed on the radiotherapy planning CT scan and subsequent follow-up CT scans and was seen to reduce by 37% at four years; the reduction was most marked in the first two years after radiotherapy. The V44 was the dosimetric parameter most significantly associated with spleen volume reduction over time ($P<0.0001$). Infectious events occurred at a rate of 16 events in 11 patients (13 episodes of pneumonia, three episodes of fatal sepsis), giving a cumulative incidence of infectious events of 16% (95% CI 4–26%) at one year and 21% (95% CI 8–33%) at four years. The incidence of pneumonia was 61.3 per 1,000 person years and the mortality rate from sepsis was 17.9 per 1,000 person years.

Accepting the limitations of such retrospective, uncontrolled studies, these two studies suggest that:[5,6]

- Radiotherapy mean doses of 5–10 Gy can cause a size reduction in the spleen
- Mean doses of >10 Gy are associated with increased rates of late infection and infection-related mortality and there may be a dose–response relationship
- Mean doses of >40 Gy may be associated with a substantially higher risk of late sepsis and sepsis-related mortality than lower doses.

Therefore, it is reasonable to consider that any patient receiving >10 Gy mean dose to the spleen may be at increased risk of late functional hyposplenism with increased rates of sepsis and sepsis-related mortality. Those receiving a mean dose to the spleen >40 Gy may be at particularly high risk.

These data represent patient cohorts where most patients received whole splenic radiotherapy. With current treatment regimens, frequently only part of the spleen is irradiated, but the clinical outcomes of partial splenic irradiation is currently unknown. Furthermore, there are no data available on the effect of hypofractionated radiotherapy regimens such as stereotactic ablative radiotherapy (SABR) on splenic size, risk of infection or infection-related mortality. Moreover, there are currently no validated tests for assessment of splenic function following radiotherapy that would allow an assessment of risk of hyposplenism for individual patients.

3. Which patients does this apply to?

This guidance applies to all patients receiving radiotherapy to the upper abdomen that results in radiotherapy dose being delivered to the spleen as part of the treatment.

Published data cannot currently support a mandatory recommendation for vaccination and antibiotic prophylaxis in all adult patients at risk of hyposplenism. There is limited information available regarding the clinical impact of radiotherapy dose to the spleen and associated long-term risks for an individual patient. As such, decision-making needs to be pragmatic. Patients should be risk-assessed as to their individual risk from splenic irradiation in the context of their malignant disease, life expectancy and co-morbidities. This should inform decisions about the appropriateness of offering vaccination and long-term antibiotic prophylaxis on an individual-patient basis.

Disease groups that should be considered include, but are not limited to:

- Sarcoma (including retroperitoneal sarcomas, spinal sarcomas, Ewing sarcoma of the rib or abdomen and any other tumours in the abdomen requiring moderate or high-dose radiotherapy)
- Lung tumours (lower lobe)
- Gastrointestinal tumours (including liver, pancreas, gastric and gastro-oesophageal junction tumours)
- Paediatric tumours (particularly Ewing sarcoma, Wilms' tumour, neuroblastoma, spinal tumours). In a series of 70 paediatric patients with a range of cancer types, the mean spleen dose was 11.3 Gy (range: 0.38–44.2 Gy)[1]
- Hodgkin and non-Hodgkin lymphoma
- Total-body irradiation
- Whole-lung radiotherapy
- SABR to lower lung or upper abdominal structures.

Internal audit data of patients treated at a single UK radiotherapy centre (UCLH, unpublished) indicate that doses and resultant risks are low for radiotherapy for:

- Breast cancer [mean splenic dose 0.5–1 Gy]
- Gynaecological tumours treating para-aortic lymph nodes [mean splenic dose 0.4–4.2 Gy]
- Pancreatic cancer [mean splenic dose 0.2–3.8 Gy].

Historical patients

There will be some patients who have received radiotherapy to the spleen in the past, putting them at risk of functional hyposplenism. Consideration should be given on an individual patient basis and in the context of the particular clinical situation as to the appropriateness of discussing this risk with the patient and implementing vaccination and lifelong antibiotic prophylaxis.

4. Information for patients

Patients who are likely to receive a mean splenic dose of >10 Gy should be risk-assessed and, if clinically appropriate, they should receive a splenic radiotherapy information leaflet and alert card.

5. Consent

The risk of functional hyposplenism and OPSI should be considered and discussed with patients likely to receive a mean splenic dose of >10 Gy; this should be included on the treatment consent form. The role of appropriate vaccination and antibiotic prophylaxis should be considered for all patients and discussed where clinically indicated. It may only become apparent that the mean splenic dose exceeds 10 Gy at the time of planning, which may then require further discussion with the patient and amendment to the consent form.

6. Critical organs and tolerance doses

There are currently no defined dose volume constraints for the spleen. There is no information on partial splenic irradiation, although the assumption is that if only a small part of the spleen is irradiated (for example, <25% and not including the hilum), splenic function may be preserved. At present, the most useful parameter to use is mean splenic dose.

The spleen should be routinely volumed as an OAR when the planning target volume (PTV) is at the same level as the spleen. The following parameters can be reported:

- Mean splenic dose (mandatory)
- V_{10Gy} (optional, to assess radiation dose homogeneity).

The aim should be to keep the mean dose to the spleen <10 Gy, if clinically appropriate. Decisions regarding the competing priorities of PTV coverage and limiting splenic dose should be made by the treating clinician. If the mean splenic dose is >10 Gy, the patient should be considered at higher risk for late functional hyposplenism and discussion of antibiotic prophylaxis and vaccination should be considered, taking into account a range of patient factors including prognosis (see section 3).

7. Recommendations

1. Immunisation and antibiotic prophylaxis for hyposplenism is an evolving field. Local hospital or regional network guidelines should be developed for patients receiving a mean splenic dose of >10 Gy, who are at higher risk for functional hyposplenism. However, the general approach should be as for other causes of hyposplenism or splenectomy.
2. Discussion with local and regional immunology and haematology specialists is advised. Useful resources to assist with guideline development for the management of these patients include the national guidelines from the British Committee for Standards in Haematology and the latest guidance from Public Health England: *Immunisations against infectious diseases – The Green Book*.[7,8]
3. If vaccinations, long-term prescription for prophylactic antibiotics and supplies of antibiotics for emergency use (according to local hyposplenism guidelines) are offered, this is likely to be best delivered by general practitioners (GPs), as is already the case for patients who have undergone surgical splenectomy. The GP must be informed that the patient has been rendered hyposplenic by radiotherapy so that they can be placed on the local register of at-risk patients.

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