Version 1.2 – 08.12.20

Clinical Oncology
The Royal College of Radiologists

RCR Guideline: Splenic radiotherapy

DRAFT

Scope

This document encompasses all patients referred for radiotherapy to the upper abdomen or an adjacent anatomical site where the upper abdomen might also be irradiated, who as a result, coincidentally receive radiotherapy to the spleen as a defined organ at risk. Treatment may be delivered using photon or proton external beam radiotherapy to a range of tumour sites.

Objective

To raise awareness of the spleen as an organ at risk structure. To ensure all patients receiving radiotherapy to the spleen have their risk of resultant functional hypo-splenism assessed, and decisions made on appropriate management if required.

Background

Patients that 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, with a mortality 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% [1-3].

The spleen is recognised to be very radiosensitive, and radiotherapy can impact on splenic function. In a study of 20,026 survivors of childhood cancer diagnosed aged ≤21 years; the long-term impact of splenic radiotherapy [mean dose to the left upper quadrant of the abdomen reconstructed from previous radiotherapy planning details] was assessed [4]. There were 62 deaths in 20,026 survivors related to sepsis (i.e. the absolute number of events was very low). Splenic radiotherapy was associated with:

- Increased late infection related mortality per 1000 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 (>10Gy) were associated with increased risk.

	Late infection related mortality (per 1000 person years)	Cumulative incidence of late infection-related mortality at 35 years	Relative risk of infection-related mortality	
Splenectomy	0.67	1.5%		7.7
Splenic RT	0.16	0.6%	0.1 – 9.9Gy 10 – 19.9Gy ≥20Gy	2.0 5.5 6.0
Neither	0.05	0.2%		

A retrospective study of 46 patients receiving post-operative chemoradiotherapy (CRT) following surgery for gastric cancer showed that 46% of patients received ≥20Gy to the spleen, with a median D_{mean} of 40Gy [5]. 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 4 years, with the reduction most marked in the first 2 years after radiotherapy. Infectious events occurred at a rate of 16 events in 11 patients (13 episodes of pneumonia, 3 episodes of fatal sepsis), giving a cumulative incidence of infectious events of 16% at 1 year, and 21% at 4 years. The incidence of pneumonia was 61.3 per 1000 person years, and a mortality rate from sepsis of 17.9 per 1000 person years.

These studies suggest that:

- Radiotherapy doses of 5 – 10 Gy can cause a size reduction in the spleen
- Doses of >10 Gy are associated with increased rates of late infection and infection-related mortality, and there appears to be a dose response relationship
- Doses of >40 Gy appear to be associated with a substantially higher risk of late sepsis and sepsis related mortality

Therefore, consider that any patient receiving >10 Gy mean dose to the spleen may be at increased risk of late functional hypo-splenism with increased rates of sepsis and sepsis related mortality. Those receiving >40 Gy may be at particularly high risk, at 35 years after radiotherapy.

1.0 Indications

1.1 All patients receiving radiotherapy to the upper abdomen which results in radiotherapy dose being delivered to the spleen as part of the treatment.

Recommendations should take into account the prognosis and estimated long-term survival rate for an individual patient, and the impact of long-term antibiotic prophylaxis and vaccination on patient quality of life. Published data supporting a mandatory recommendation in adult patients are limited, and there are no data on hypo-fractionated radiotherapy regimens. Therefore decision-making, by necessity, needs to be pragmatic because of the limited nature of the available information on the clinical impact of radiotherapy dose to the spleen and associated long-term risks for an individual patient. Patients should be risk-assessed as to their individual risk from splenic irradiation in the context of their disease, life expectancy and co-morbidities, and decisions made as to appropriateness of offering vaccination and long-term antibiotic prophylaxis.

1.2 Patient groups who particularly need to 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 median mean spleen dose was 11.3 Gy (range: 0.38-44.2 Gy) [ref].
- Hodgkin and non-Hodgkin lymphoma

- Total Body irradiation
- Whole lung radiotherapy
- Stereotactic ablative 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 -1Gy], gynaecological tumours treating para-aortic lymph nodes [mean splenic dose 0.4 – 4.2Gy], and pancreatic cancer [mean splenic dose 0.2 – 3.8Gy].

1.3 Historical patients – there will be some patients who have received radiotherapy to the spleen in the past, rendering them at risk of functional hypo-splenism. Consideration should be given, on an individual 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.

2.0 Information for Patients

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

3.0 Consent

3.1 For patients likely to receive a mean splenic dose of >10 Gy, the risk of functional hypo-splenism and risk of OPSI (particularly for patient receiving >40Gy) should be considered and discussed with the patient, and included on the 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, in which case this may require further discussion with the patient at that point and the consent form may require amendment.

4.0 Critical Organs and Tolerance Doses

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

For patients with PTV on the same level as the spleen, it should be routinely volumed as an organ at risk. The following parameters should be routinely reported:

- Mean splenic dose
- V_{10Gy}

The aim should be to keep the mean dose to the spleen <10 Gy, if clinically appropriate. The decision as to 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 hypo-splenism and discussion of antibiotic

prophylaxis and vaccination should be considered, taking into account a range of patient factors including prognosis.

5.0 Recommendations

Immunisation and antibiotic prophylaxis for hypo-splenism 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 hypo-splenism. However, the general approach should be as for other causes of hypo-splenism or splenectomy.

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[6] and the latest guidance from Public Health England: Immunisations against infectious diseases – The Green Book. Available at: https://www.gov.uk/government/publications/immunisation-of-individuals-with-underlying-medical-conditions-the-green-book-chapter-7

If vaccinations, long-term prescription for prophylactic antibiotics and supplies of antibiotics for emergency use (according to local hypo-splenism guidelines) are offered, this is likely to be best delivered by GPs, as is already the case for patients who have undergone surgical splenectomy. It is strongly recommend to inform the GP that the patient has been rendered hypo-splenic by radiotherapy so that they can be placed on the local register of at-risk patients.

References

1. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet* 2011; **378**(9785): 86-97.

2. de Porto AP, Lammers AJ, Bennink RJ, ten Berge IJ, Speelman P, Hoekstra JB. Assessment of splenic function. *Eur J Clin Microbiol Infect Dis* 2010; **29**(12): 1465-73.

3. Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. *N Engl J Med* 2014; **371**(4): 349-56.

4. Weil BR, Madenci AL, Liu Q, et al. Late Infection-Related Mortality in Asplenic Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol* 2018; **36**(16): 1571-8.

5. Trip AK, Sikorska K, van Sandick JW, et al. Radiation-induced dose dependent changes of the spleen following postoperative chemoradiotherapy for gastric cancer. *Radiother Oncol* 2015; **116**(2): 239-44.

6. Davies JM, Lewis MP, Wimperis J, Rafi I, Ladhani S, Bolton-Maggs PH. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: prepared on behalf of the British Committee for Standards in Haematology by a working party of the Haemato-Oncology task force. *Br J Haematol* 2011; **155**(3): 308-17.

Additional reference:
Niruthiga Arunagiri, Sarah M. Kelly, Cathy Dunlea, Olivia Dixon, Jessica Cantwell, Pravesh Bhudia, Tom Boterberg, Geert O. Janssens, Jennifer E. Gains, Yen-Ch'ing Chang, Mark N. Gaze on behalf of the SIOP-Europe Radiation Oncology Working Group. The spleen as an organ at risk in paediatric radiotherapy: A SIOP-Europe Radiation Oncology Working Group report *European Journal of Cancer* 2021, **143**: 1-10.
https://doi.org/10.1016/j.ejca.2020.10.025