

# [Bystander effects and unintended consequences: time to include the spleen in radi...](https://assignbuster.com/bystander-effects-and-unintended-consequences-time-to-include-the-spleen-in-radiation-therapy-planning/)

[Health & Medicine](https://assignbuster.com/essay-subjects/health-n-medicine/)

During residency through 2003, I learned about the historical role of radiation treating the spleen on the lymphoma service, including use of low-dose radiation as palliative treatment with potential significant toxicity ( [1](#B1) ). But when treating gastrointestinal malignancies, there was no research at the time indicating concern about the potential effects of splenic irradiation. As radiation therapy has evolved over the past two decades, our ability to accurately shape high dose radiation fields has improved substantially.

In the era of intensity modulated radiation therapy (IMRT) and stereotactic body radiotherapy (SBRT), we have mostly ignored the spleen until recently. The time has come to contour it, so that treatment planning systems include splenic dose in plan optimization because of its potential to help or harm our patients.

## Spleen as Innocent Bystander

As IMRT use increased, the question became meaningful enough that I reviewed a small number of patients receiving abdominal radiation at my hospital 2007-8 and found a Dmean of 19 Gy and V20Gy of 82% for distal esophageal cancer patients ( [2](#B2) ). We didn't have enough patients to look at clinical outcomes but that seemed like a meaningful dose particularly for immune cells and spleen function. Reviewing the literature, I learned that Drs. C. Norman Coleman and Henry Kaplan identified splenic atrophy with radiation therapy in 1980 ( [3](#B3) ), subsequently demonstrating organ injury and a risk of sepsis ( [4](#B4) , [5](#B5) ). There are well-documented risks of sepsis after splenectomy ( [6](#B6) ), and I didn't want the radiation to contribute to that risk. Since 2011, I have recommended pneumococcal vaccinations for my patients with upper abdominal malignancies before receiving chemoradiation on first principles, initially in the absence of any good data. Recent research confirms an association with higher splenic doses and risk of infection in pediatric cancer survivors that only increases with time, suggesting immunization has value ( [7](#B7) ).

Over the past decade, QUANTEC provided no guidance at all ( [8](#B8) ). RTOG consensus contouring guidelines show it in the figures but don't mention any detail ( [9](#B9) ). If the physician or dosimetrist doesn't contour and place constraints on the spleen, treatment planning system software will consider the spleen a safe part of the body to push dose to avoid other important intra-abdominal organs.

Now, there are increasing data emerging suggesting that we should care about potential negative effects of splenic radiation with solid malignancies. In gastric cancer, a small study showed chemoradiation had a splenic D mean of 40 Gy with mean 37% volume loss and a high risk of pneumonia ( [10](#B10) ). For esophageal cancer chemoradiation, higher spleen dose is associated with a higher risk of lymphopenia in one study and lower toxicity in another ( [11](#B11) , [12](#B12) ). Distal esophageal cancers and larger irradiated volumes are more likely to have severe lymphopenia, suggesting lower dose to normal tissue may matter ( [13](#B13) , [14](#B14) ). Lymphopenia is also associated with lower survival ( [13](#B13) ). Similar data are emerging in pancreatic cancer chemoradiation ( [15](#B15) – [18](#B18) ), with lower rates of lymphopenia using stereotactic body techniques ( [19](#B19) , [20](#B20) ). Splenic dose may also be clinically relevant in hepatoma ( [21](#B21) ).

Lung cancer research has mostly ignored potential splenic radiation toxicity. One study suggests decreased spleen volume with chemoradiation for non-small cell lung cancer but did not look at spleen dose or location of the primary tumor ( [22](#B22) ). Some interest in bone marrow toxicity has focused upon the vertebral bodies without evaluating splenic dose ( [23](#B23) , [24](#B24) ). Cardiac dose and lung also has been associated with hematologic toxicity but did not assess the spleen or primary tumor location ( [25](#B25) , [26](#B26) ). It is possible that the association of lymphopenia with higher cardiac dose occurs in left lower lobe primary tumors, where the spleen may also receive higher doses. Without including the spleen in treatment planning, any potential detrimental effects for lung cancer patients will remain unknown.

## A Role in Cancer Control?

The spleen also may play an important role in effective cancer treatment, especially in the immunotherapy era ( [27](#B27) ). Treatment-related lymphopenia is associated with worse disease progression and survival in esophageal, pancreatic, and lung cancer ( [13](#B13) , [16](#B16) , [28](#B28) – [30](#B30) ). The spleen is an important source of tumor-associated macrophages and neutrophils ( [31](#B31) ), which may contribute to tumor progression and death via decreased immune surveillance or pro-inflammatory stimulation for tumor growth ( [32](#B32) – [37](#B37) ). Radiation can also induce regulatory T cells ( [38](#B38) ), which may alter peripheral blood immunophenotype in a tissue-specific fashion ( [39](#B39) ).

Based upon the currently published literature, I can't predict what low doses of splenic radiation may do to worsen or improve cancer control. But it seems the spleen deserves more attention if it could help lessen treatment toxicity and may factor into efficacy.

Our treatment planning systems will not consider the spleen of any clinical value unless we do. The time has come to seriously evaluate splenic dose in solid malignancies. We have ample opportunity for more retrospective and prospective studies so we can learn how to better address the immunologic health of our patients receiving radiation therapy.

## Author Contributions

The author confirms being the sole contributor of this work and has approved it for publication.

## Conflict of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

1. Weinmann M, Becker G, Einsele H, Bamberg M. Clinical indications and biological mechanisms of splenic irradiation in chronic leukaemias and myeloproliferative disorders. *Radiother Oncol.* (2001) 58: 235–46. doi: 10. 1016/S0167-81400000316-9

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/11230883) | [CrossRef Full Text](https://doi.org/10.1016/S0167-81400000316-9) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Weinmann&author=G.+Becker&author=H.+Einsele&author=M.+Bamberg+&publication_year=2001&title=Clinical+indications+and+biological+mechanisms+of+splenic+irradiation+in+chronic+leukaemias+and+myeloproliferative+disorders&journal=Radiother+Oncol.&volume=58&pages=235-46)

2. Katz M, McKee AB, MacDonald BA, Sirois L, Gagne FM, Knab BR. *Splenic Dose With Abdominal Radiation Therapy: A Quantitative Dosimetric Study.* (2011). Slideshare. com. Available online at: [https://www. slideshare. net/subatomicdoc/splenic-dose-with-abdominal-radiation-therapy](https://www.slideshare.net/subatomicdoc/splenic-dose-with-abdominal-radiation-therapy)

3. Dailey MO, Coleman CN, Kaplan HS. Radiation-induced splenic atrophy in patients with Hodgkin's disease and non-Hodgkin's lymphomas. *N Engl J Med.* (1980) 302: 215–7. doi: 10. 1056/NEJM198001243020406

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/7350461) | [CrossRef Full Text](https://doi.org/10.1056/NEJM198001243020406) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MO.+Dailey&author=CN.+Coleman&author=HS.+Kaplan+&publication_year=1980&title=Radiation-induced+splenic+atrophy+in+patients+with+Hodgkin's+disease+and+non-Hodgkin's+lymphomas&journal=N+Engl+J+Med.&volume=302&pages=215-7)

4. Dailey MO, Coleman CN, Fajardo LF. Splenic injury caused by therapeutic radiation. *Am J Surg Pathol.* (1981) 5: 325–31. doi: 10. 1097/00000478-198106000-00002

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/7270781) | [CrossRef Full Text](https://doi.org/10.1097/00000478-198106000-00002) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MO.+Dailey&author=CN.+Coleman&author=LF.+Fajardo+&publication_year=1981&title=Splenic+injury+caused+by+therapeutic+radiation&journal=Am+J+Surg+Pathol.&volume=5&pages=325-31)

5. Coleman CN, McDougall IR, Dailey MO, Ager P, Bush S, Kaplan HS. Functional hyposplenia after splenic irradiation for Hodgkin's disease. *Ann Intern Med* . (1982) 96: 44–7. doi: 10. 7326/0003-4819-96-1-44

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/7053701) | [CrossRef Full Text](https://doi.org/10.7326/0003-4819-96-1-44) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=CN.+Coleman&author=IR.+McDougall&author=MO.+Dailey&author=P.+Ager&author=S.+Bush&author=HS.+Kaplan+&publication_year=1982&title=Functional+hyposplenia+after+splenic+irradiation+for+Hodgkin's+disease&journal=Ann+Intern+Med&volume=96&pages=44-7)

6. Ram S, Lewis LA, Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. *Clin Microbiol Rev.* (2010) 23: 740–80. doi: 10. 1128/CMR. 00048-09

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/20930072) | [CrossRef Full Text](https://doi.org/10.1128/CMR.00048-09) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Ram&author=LA.+Lewis&author=PA.+Rice+&publication_year=2010&title=Infections+of+people+with+complement+deficiencies+and+patients+who+have+undergone+splenectomy&journal=Clin+Microbiol+Rev.&volume=23&pages=740-80)

7. Weil BR, Madenci AL, Liu Q, Howell RM, Gibson TM, Yasui Y, 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: 1571–8. doi: 10. 1200/JCO. 2017. 76. 1643

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29664715) | [CrossRef Full Text](https://doi.org/10.1200/JCO.2017.76.1643) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=BR.+Weil&author=AL.+Madenci&author=Q.+Liu&author=RM.+Howell&author=TM.+Gibson&author=Y.+Yasui+&publication_year=2018&title=Late+infection-related+mortality+in+asplenic+survivors+of+childhood+cancer%3A+a+report+from+the+Childhood+Cancer+Survivor+Study&journal=J+Clin+Oncol.&volume=36&pages=1571-8)

8. Marks LB, Ten Haken RK, Martel MK. Guest editor's introduction to QUANTEC: a user's guide. *Int J Radiat Oncol Biol Phys.* (2010) 76(3 Suppl.): S1–2. doi: 10. 1016/j. ijrobp. 2009. 08. 075

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/20171501) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2009.08.075) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=LB.+Marks&author=RK.+Ten+Haken&author=MK.+Martel+&publication_year=2010&title=Guest+editor's+introduction+to+QUANTEC%3A+a+user's+guide&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=76&pages=S1-2)

9. Trip AK, Sikorska K, van Sandick JW, Heeg M, Cats A, Boot H, et al. Radiation-induced dose-dependent changes of the spleen following postoperative chemoradiotherapy for gastric cancer. *Radiother Oncol.* (2015) 116: 239–44. doi: 10. 1016/j. radonc. 2015. 07. 036

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26253953) | [CrossRef Full Text](https://doi.org/10.1016/j.radonc.2015.07.036) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AK.+Trip&author=K.+Sikorska&author=JW.+van+Sandick&author=M.+Heeg&author=A.+Cats&author=H.+Boot+&publication_year=2015&title=Radiation-induced+dose-dependent+changes+of+the+spleen+following+postoperative+chemoradiotherapy+for+gastric+cancer&journal=Radiother+Oncol.&volume=116&pages=239-44)

10. Jabbour SK, Hashem SA, Bosch W, Kim TK, Finkelstein SE, Anderson BM, et al. Upper abdominal normal organ contouring guidelines and atlas: a Radiation Therapy Oncology Group consensus. *Pract Radiat Oncol.* (2014) 4: 82–9. doi: 10. 1016/j. prro. 2013. 06. 004

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/24890348) | [CrossRef Full Text](https://doi.org/10.1016/j.prro.2013.06.004) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=SK.+Jabbour&author=SA.+Hashem&author=W.+Bosch&author=TK.+Kim&author=SE.+Finkelstein&author=BM.+Anderson+&publication_year=2014&title=Upper+abdominal+normal+organ+contouring+guidelines+and+atlas%3A+a+Radiation+Therapy+Oncology+Group+consensus&journal=Pract+Radiat+Oncol.&volume=4&pages=82-9)

11. Saito T, Toya R, Yoshida N, Shono T, Matsuyama T, Ninomura S, et al. Spleen dose-volume parameters as a predictor of treatment-related lymphopenia during definitive chemoradiotherapy for esophageal cancer. *In Vivo.* (2018) 32: 1519–25. doi: 10. 21873/invivo. 11409

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30348711) | [CrossRef Full Text](https://doi.org/10.21873/invivo.11409) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=T.+Saito&author=R.+Toya&author=N.+Yoshida&author=T.+Shono&author=T.+Matsuyama&author=S.+Ninomura+&publication_year=2018&title=Spleen+dose-volume+parameters+as+a+predictor+of+treatment-related+lymphopenia+during+definitive+chemoradiotherapy+for+esophageal+cancer&journal=In+Vivo.&volume=32&pages=1519-25)

12. Chin AL, Aggarwal S, Pradhan P, Bush K, von Eyben R, Koong AC, et al. The role of bone marrow and spleen irradiation in the development of acute hematologic toxicity during chemoradiation for esophageal cancer. *Adv Radiat Oncol.* (2018) 3: 297–304. doi: 10. 1016/j. adro. 2018. 02. 005

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30202799) | [CrossRef Full Text](https://doi.org/10.1016/j.adro.2018.02.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AL.+Chin&author=S.+Aggarwal&author=P.+Pradhan&author=K.+Bush&author=R.+von+Eyben&author=AC.+Koong+&publication_year=2018&title=The+role+of+bone+marrow+and+spleen+irradiation+in+the+development+of+acute+hematologic+toxicity+during+chemoradiation+for+esophageal+cancer&journal=Adv+Radiat+Oncol.&volume=3&pages=297-304)

13. van Rossum PSN, Deng W, Routman DM, Liu AY, Xu C, Shiraishi Y, et al. Prediction of severe lymphopenia during chemoradiation therapy for esophageal cancer: development and validation of a pretreatment nomogram. *Pract Radiat Oncol.* (2019) 10: e16–26. doi: 10. 1016/j. prro. 2019. 07. 010

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31369887) | [CrossRef Full Text](https://doi.org/10.1016/j.prro.2019.07.010) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=PSN.+van+Rossum&author=W.+Deng&author=DM.+Routman&author=AY.+Liu&author=C.+Xu&author=Y.+Shiraishi+&publication_year=2019&title=Prediction+of+severe+lymphopenia+during+chemoradiation+therapy+for+esophageal+cancer%3A+development+and+validation+of+a+pretreatment+nomogram&journal=Pract+Radiat+Oncol.&volume=10&pages=e16-26)

14. Davuluri R, Jiang W, Fang P, Xu C, Komaki R, Gomez DR, et al. Lymphocyte nadir and esophageal cancer survival outcomes after chemoradiation therapy. *Int J Radiat Oncol Biol Phys.* (2017) 99: 128–35. doi: 10. 1016/j. ijrobp. 2017. 05. 037

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28816138) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2017.05.037) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=R.+Davuluri&author=W.+Jiang&author=P.+Fang&author=C.+Xu&author=R.+Komaki&author=DR.+Gomez+&publication_year=2017&title=Lymphocyte+nadir+and+esophageal+cancer+survival+outcomes+after+chemoradiation+therapy&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=99&pages=128-35)

15. Chadha AS, Liu G, Chen HC, Das P, Minsky BD, Mahmood U, et al. Does unintentional splenic radiation predict outcomes after pancreatic cancer radiation therapy? *Int J Radiat Oncol Biol Phys.* (2017) 97: 323–32. doi: 10. 1016/j. ijrobp. 2016. 10. 046

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28068240) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2016.10.046) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AS.+Chadha&author=G.+Liu&author=HC.+Chen&author=P.+Das&author=BD.+Minsky&author=U.+Mahmood+&publication_year=2017&title=Does+unintentional+splenic+radiation+predict+outcomes+after+pancreatic+cancer+radiation+therapy%3F&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=97&pages=323-32)

16. Zschaeck S, Blümke B, Wust P, Kaul D, Bahra M, Riess H, et al. Dose-escalated radiotherapy for unresectable or locally recurrent pancreatic cancer: dose volume analysis, toxicity and outcome of 28 patients. *PLoS ONE.* (2017) 12: e0186341. doi: 10. 1371/journal. pone. 0186341

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29023527) | [CrossRef Full Text](https://doi.org/10.1371/journal.pone.0186341) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Zschaeck&author=B.+Blümke&author=P.+Wust&author=D.+Kaul&author=M.+Bahra&author=H.+Riess+&publication_year=2017&title=Dose-escalated+radiotherapy+for+unresectable+or+locally+recurrent+pancreatic+cancer%3A+dose+volume+analysis,+toxicity+and+outcome+of+28+patients&journal=PLoS+ONE.&volume=12&pages=e0186341)

17. Balmanoukian A, Ye X, Herman J, Laheru D, Grossman SA. The association between treatment-related lymphopenia and survival in newly diagnosed patients with resected adenocarcinoma of the pancreas. *Cancer Invest.* (2012) 30: 571–6. doi: 10. 3109/07357907. 2012. 700987

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/22812722) | [CrossRef Full Text](https://doi.org/10.3109/07357907.2012.700987) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Balmanoukian&author=X.+Ye&author=J.+Herman&author=D.+Laheru&author=SA.+Grossman+&publication_year=2012&title=The+association+between+treatment-related+lymphopenia+and+survival+in+newly+diagnosed+patients+with+resected+adenocarcinoma+of+the+pancreas&journal=Cancer+Invest.&volume=30&pages=571-6)

18. Wild AT, Ye X, Ellsworth SG, Smith JA, Narang AK, Garg T, et al. The association between chemoradiation–related lymphopenia and clinical outcomes in patients with locally advanced pancreatic adenocarcinoma. *Am J Clin Oncol.* (2015) 38: 259–65. doi: 10. 1097/COC. 0b013e3182940ff9

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/23648440) | [CrossRef Full Text](https://doi.org/10.1097/COC.0b013e3182940ff9) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AT.+Wild&author=X.+Ye&author=SG.+Ellsworth&author=JA.+Smith&author=AK.+Narang&author=T.+Garg+&publication_year=2015&title=The+association+between+chemoradiation–related+lymphopenia+and+clinical+outcomes+in+patients+with+locally+advanced+pancreatic+adenocarcinoma&journal=Am+J+Clin+Oncol.&volume=38&pages=259-65)

19. Wild AT, Herman JM, Dholakia AS, Moningi S, Lu Y, Rosati LM, et al. Lymphocyte-sparing effect of stereotactic body radiation therapy in patients with unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys.* (2016) 94: 571–9. doi: 10. 1016/j. ijrobp. 2015. 11. 026

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26867885) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2015.11.026) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AT.+Wild&author=JM.+Herman&author=AS.+Dholakia&author=S.+Moningi&author=Y.+Lu&author=LM.+Rosati+&publication_year=2016&title=Lymphocyte-sparing+effect+of+stereotactic+body+radiation+therapy+in+patients+with+unresectable+pancreatic+cancer&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=94&pages=571-9)

20. Wu G, Baine MJ, Zhao N, Li S, Li X, Lin C. Lymphocyte-sparing effect of stereotactic body radiation therapy compared to conventional fractionated radiation therapy in patients with locally advanced pancreatic cancer. *BMC Cancer.* (2019) 19: 977. doi: 10. 1186/s12885-019-6220-1

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31640607) | [CrossRef Full Text](https://doi.org/10.1186/s12885-019-6220-1) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=G.+Wu&author=MJ.+Baine&author=N.+Zhao&author=S.+Li&author=X.+Li&author=C.+Lin+&publication_year=2019&title=Lymphocyte-sparing+effect+of+stereotactic+body+radiation+therapy+compared+to+conventional+fractionated+radiation+therapy+in+patients+with+locally+advanced+pancreatic+cancer&journal=BMC+Cancer.&volume=19&pages=977)

21. Liu J, Zhao Q, Deng W, Lu J, Xu X, Wang R, et al. Radiation-related lymphopenia is associated with spleen irradiation dose during radiotherapy in patients with hepatocellular carcinoma. *Radiat Oncol.* (2017) 12: 90. doi: 10. 1186/s13014-017-0824-x

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28558844) | [CrossRef Full Text](https://doi.org/10.1186/s13014-017-0824-x) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=J.+Liu&author=Q.+Zhao&author=W.+Deng&author=J.+Lu&author=X.+Xu&author=R.+Wang+&publication_year=2017&title=Radiation-related+lymphopenia+is+associated+with+spleen+irradiation+dose+during+radiotherapy+in+patients+with+hepatocellular+carcinoma&journal=Radiat+Oncol.&volume=12&pages=90)

22. Wen SW, Everitt SJ, Bedo J, Chabrot M, Ball DL, Solomon B, et al. Spleen volume variation in patients with locally advanced non-small cell lung cancer receiving platinum-based chemo-radiotherapy. *PLoS ONE.* (2015) 10: e142608. doi: 10. 1371/journal. pone. 0142608

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26599227) | [CrossRef Full Text](https://doi.org/10.1371/journal.pone.0142608) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=SW.+Wen&author=SJ.+Everitt&author=J.+Bedo&author=M.+Chabrot&author=DL.+Ball&author=B.+Solomon+&publication_year=2015&title=Spleen+volume+variation+in+patients+with+locally+advanced+non-small+cell+lung+cancer+receiving+platinum-based+chemo-radiotherapy&journal=PLoS+ONE.&volume=10&pages=e142608)

23. Deek MP, Benenati B, Kim S, Chen T, Ahmed I, Zou W, et al. Thoracic vertebral body irradiation contributes to acute hematologic toxicity during chemoradiation therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* (2016) 94: 147–54. doi: 10. 1016/j. ijrobp. 2015. 09. 022

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26700708) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2015.09.022) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MP.+Deek&author=B.+Benenati&author=S.+Kim&author=T.+Chen&author=I.+Ahmed&author=W.+Zou+&publication_year=2016&title=Thoracic+vertebral+body+irradiation+contributes+to+acute+hematologic+toxicity+during+chemoradiation+therapy+for+non-small+cell+lung+cancer&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=94&pages=147-54)

24. Barney CL, Scoville N, Allan E, Ayan A, DiCostanzo D, Haglund KE, et al. Radiation dose to the thoracic vertebral bodies is associated with acute hematologic toxicities in patients receiving concurrent chemoradiation for lung cancer: results of a single-center retrospective analysis. *Int J Radiat Oncol Biol Phys.* (2018) 100: 748–55. doi: 10. 1016/j. ijrobp. 2017. 11. 025

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29413286) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2017.11.025) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=CL.+Barney&author=N.+Scoville&author=E.+Allan&author=A.+Ayan&author=D.+DiCostanzo&author=KE.+Haglund+&publication_year=2018&title=Radiation+dose+to+the+thoracic+vertebral+bodies+is+associated+with+acute+hematologic+toxicities+in+patients+receiving+concurrent+chemoradiation+for+lung+cancer%3A+results+of+a+single-center+retrospective+analysis&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=100&pages=748-55)

25. Contreras JA, Lin AJ, Weiner A, Speirs C, Samson P, Mullen D, et al. Cardiac dose is associated with immunosuppression and poor survival in locally advanced non-small cell lung cancer. *Radiother Oncol.* (2018) 128: 498–504. doi: 10. 1016/j. radonc. 2018. 05. 017

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29859754) | [CrossRef Full Text](https://doi.org/10.1016/j.radonc.2018.05.017) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=JA.+Contreras&author=AJ.+Lin&author=A.+Weiner&author=C.+Speirs&author=P.+Samson&author=D.+Mullen+&publication_year=2018&title=Cardiac+dose+is+associated+with+immunosuppression+and+poor+survival+in+locally+advanced+non-small+cell+lung+cancer&journal=Radiother+Oncol.&volume=128&pages=498-504)

26. Tang C, Liao Z, Gomez D, Levy L, Zhuang Y, Gebremichael RA, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. *Int J Radiat Oncol Biol Phys.* (2014) 89: 1084–91. doi: 10. 1016/j. ijrobp. 2014. 04. 025

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/25035212) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2014.04.025) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=C.+Tang&author=Z.+Liao&author=D.+Gomez&author=L.+Levy&author=Y.+Zhuang&author=RA.+Gebremichael+&publication_year=2014&title=Lymphopenia+association+with+gross+tumor+volume+and+lung+V5+and+its+effects+on+non-small+cell+lung+cancer+patient+outcomes&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=89&pages=1084-91)

27. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC. *N Engl J Med.* (2018) 379: 2342–50. doi: 10. 1056/NEJMoa1809697

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30280658) | [CrossRef Full Text](https://doi.org/10.1056/NEJMoa1809697) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=SJ.+Antonia&author=A.+Villegas&author=D.+Daniel&author=D.+Vicente&author=S.+Murakami&author=R.+Hui+&publication_year=2018&title=Overall+survival+with+durvalumab+after+chemoradiotherapy+in+Stage+III+NSCLC&journal=N+Engl+J+Med.&volume=379&pages=2342-50)

28. Zhou XL, Zhu WG, Zhu ZJ, Wang WW, Deng X, Tao WJ, et al. Lymphopenia is esophageal squamous cell carcinoma: relationship to malnutrition, various disease parameters, and response to concurrent chemoradiotherapy. *Oncologist.* (2019) 24: e677–86. doi: 10. 1634/theoncologist. 2018-0723

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31040254) | [CrossRef Full Text](https://doi.org/10.1634/theoncologist.2018-0723) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=XL.+Zhou&author=WG.+Zhu&author=ZJ.+Zhu&author=WW.+Wang&author=X.+Deng&author=WJ.+Tao+&publication_year=2019&title=Lymphopenia+is+esophageal+squamous+cell+carcinoma%3A+relationship+to+malnutrition,+various+disease+parameters,+and+response+to+concurrent+chemoradiotherapy&journal=Oncologist.&volume=24&pages=e677-86)

29. Ladbury CJ, Rusthoven CG, Camidge DR, Kavanagh BD, Nath SK. Impact of radiation dose to the host immune system on tumor control and survival for Stage III non-small cell lung cancer treated with definitive radiation therapy. *Int J Radiat Oncol Biol Phys.* (2019) 105: 346–55. doi: 10. 1016/j. ijrobp. 2019. 05. 064

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31175902) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2019.05.064) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=CJ.+Ladbury&author=CG.+Rusthoven&author=DR.+Camidge&author=BD.+Kavanagh&author=SK.+Nath+&publication_year=2019&title=Impact+of+radiation+dose+to+the+host+immune+system+on+tumor+control+and+survival+for+Stage+III+non-small+cell+lung+cancer+treated+with+definitive+radiation+therapy&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=105&pages=346-55)

30. Cho O, Oh YT, Chun M, Noh OK, Lee HW. Radiation-related lymphopenia as a new prognostic factor in limited-stage small cell lung cancer. *Tumour Biol.* (2016) 37: 971–8. doi: 10. 1007/s13277-015-3888-y

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26264618) | [CrossRef Full Text](https://doi.org/10.1007/s13277-015-3888-y) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=O.+Cho&author=YT.+Oh&author=M.+Chun&author=OK.+Noh&author=HW.+Lee+&publication_year=2016&title=Radiation-related+lymphopenia+as+a+new+prognostic+factor+in+limited-stage+small+cell+lung+cancer&journal=Tumour+Biol.&volume=37&pages=971-8)

31. Cortez-Retamozo V, Etzrodt M, Newton A, Rauch PJ, Chudnovskiy A, Berger C, et al. Origins of tumor-associated macrophages and neutrophils. *Proc Natl Acad Sci USA.* (2012) 109: 2491–6. doi: 10. 1073/pnas. 1113744109

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/22308361) | [CrossRef Full Text](https://doi.org/10.1073/pnas.1113744109) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Cortez-Retamozo&author=M.+Etzrodt&author=A.+Newton&author=PJ.+Rauch&author=A.+Chudnovskiy&author=C.+Berger+&publication_year=2012&title=Origins+of+tumor-associated+macrophages+and+neutrophils&journal=Proc+Natl+Acad+Sci+USA.&volume=109&pages=2491-6)

32. Wisdom AJ, Hong CS, Lin AJ, Xiang Y, Cooper DE, Zhang J, et al. Neutrophils promote tumor resistance to radiation therapy. *Proc Natl Acad Sci USA.* (2019) 116: 18584–9. doi: 10. 1073/pnas. 1901562116

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31462499) | [CrossRef Full Text](https://doi.org/10.1073/pnas.1901562116) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AJ.+Wisdom&author=CS.+Hong&author=AJ.+Lin&author=Y.+Xiang&author=DE.+Cooper&author=J.+Zhang+&publication_year=2019&title=Neutrophils+promote+tumor+resistance+to+radiation+therapy&journal=Proc+Natl+Acad+Sci+USA.&volume=116&pages=18584-9)

33. Cox S, Hurt C, Grenader T, Mukherjee S, Bridgewater J, Crosby T. The prognostic value of derived neutrophil to lymphocyte ratio in oesophageal cancer treated with definitive chemoradiotherapy. *Radiother Oncol.* (2017) 125: 154–9. doi: 10. 1016/j. radonc. 2017. 08. 023

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28893415) | [CrossRef Full Text](https://doi.org/10.1016/j.radonc.2017.08.023) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Cox&author=C.+Hurt&author=T.+Grenader&author=S.+Mukherjee&author=J.+Bridgewater&author=T.+Crosby+&publication_year=2017&title=The+prognostic+value+of+derived+neutrophil+to+lymphocyte+ratio+in+oesophageal+cancer+treated+with+definitive+chemoradiotherapy&journal=Radiother+Oncol.&volume=125&pages=154-9)

34. Scilla KA, Bentzen SM, Lam VK, Mohindra P, Nichols EM, Vyfhuis MA, et al. Neutrophil-lymphocyte ratio is a prognostic marker in patients with locally advanced (Stage IIIA and IIIB) non-small cell lung cancer treated with combined modality therapy. *Oncologist.* (2017) 22: 737–42. doi: 10. 1634/theoncologist. 2016-0443

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28533476) | [CrossRef Full Text](https://doi.org/10.1634/theoncologist.2016-0443) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=KA.+Scilla&author=SM.+Bentzen&author=VK.+Lam&author=P.+Mohindra&author=EM.+Nichols&author=MA.+Vyfhuis+&publication_year=2017&title=Neutrophil-lymphocyte+ratio+is+a+prognostic+marker+in+patients+with+locally+advanced+(Stage+IIIA+and+IIIB)+non-small+cell+lung+cancer+treated+with+combined+modality+therapy&journal=Oncologist.&volume=22&pages=737-42)

35. Pike LRG, Bang A, Mahal BA, Taylor A, Krishnan M, Spektor A, et al. The impact of radiation therapy on lymphocyte count and survival in metastatic cancer patients receiving PD-1 immune checkpoint inhibitors. *Int J Radiat Oncol Biol Phys.* (2019) 103: 142–51. doi: 10. 1016/j. ijrobp. 2018. 09. 010

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30227198) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2018.09.010) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=LRG.+Pike&author=A.+Bang&author=BA.+Mahal&author=A.+Taylor&author=M.+Krishnan&author=A.+Spektor+&publication_year=2019&title=The+impact+of+radiation+therapy+on+lymphocyte+count+and+survival+in+metastatic+cancer+patients+receiving+PD-1+immune+checkpoint+inhibitors&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=103&pages=142-51)

36. Sebastian N, Wu T, Bazan J, Driscoll E, Willers H, Yegya-Raman N, et al. Pre-treatment neutrophil-lymphocyte ratio is associated with overall mortality in localized non-small cell lung cancer treated with stereotactic body radiotherapy. *Radiother Oncol.* (2019) 134: 151–7. doi: 10. 1016/j. radonc. 2019. 01. 032

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31005209) | [CrossRef Full Text](https://doi.org/10.1016/j.radonc.2019.01.032) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+Sebastian&author=T.+Wu&author=J.+Bazan&author=E.+Driscoll&author=H.+Willers&author=N.+Yegya-Raman+&publication_year=2019&title=Pre-treatment+neutrophil-lymphocyte+ratio+is+associated+with+overall+mortality+in+localized+non-small+cell+lung+cancer+treated+with+stereotactic+body+radiotherapy&journal=Radiother+Oncol.&volume=134&pages=151-7)

37. Rakaee M, Busund LR, Jamaly S, Paulsen EE, Richardsen E, Andersen S, et al. Prognostic value of macrophage phenotypes in resectable non-small cell lung cancer assessed by multiplex immunohistochemistry. *Neoplasia.* (2019) 21: 282–93. doi: 10. 1016/j. neo. 2019. 01. 005

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30743162) | [CrossRef Full Text](https://doi.org/10.1016/j.neo.2019.01.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=M.+Rakaee&author=LR.+Busund&author=S.+Jamaly&author=EE.+Paulsen&author=E.+Richardsen&author=S.+Andersen+&publication_year=2019&title=Prognostic+value+of+macrophage+phenotypes+in+resectable+non-small+cell+lung+cancer+assessed+by+multiplex+immunohistochemistry&journal=Neoplasia.&volume=21&pages=282-93)

38. Wirsdörfer F, Cappuccini F, Niazman M, de Leve S, Westendorf AM, Lüdemann L, et al. Thorax irradiation triggers a local and systemic accumulation of immunosuppressive CD4+ FoxP3+ regulatory T cells. *Radiat Oncol.* (2014) 9: 98. doi: 10. 1186/1748-717X-9-98

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/24766907) | [CrossRef Full Text](https://doi.org/10.1186/1748-717X-9-98) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=F.+Wirsdörfer&author=F.+Cappuccini&author=M.+Niazman&author=S.+de+Leve&author=AM.+Westendorf&author=L.+Lüdemann+&publication_year=2014&title=Thorax+irradiation+triggers+a+local+and+systemic+accumulation+of+immunosuppressive+CD4++FoxP3++regulatory+T+cells&journal=Radiat+Oncol.&volume=9&pages=98)

39. McGee HM, Daly ME, Azghadi S, Stewart SL, Oesterich L, Schlom J, et al. Stereotactic ablative radiation therapy induces systemic differences in peripheral blood immunophenotype dependent upon irradiated site. *Int J Radiat Oncol Biol Phys.* (2018) 101: 1259–70. doi: 10. 1016/j. ijrobp. 2018. 04. 038

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29891204) | [CrossRef Full Text](https://doi.org/10.1016/j.ijrobp.2018.04.038) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=HM.+McGee&author=ME.+Daly&author=S.+Azghadi&author=SL.+Stewart&author=L.+Oesterich&author=J.+Schlom+&publication_year=2018&title=Stereotactic+ablative+radiation+therapy+induces+systemic+differences+in+peripheral+blood+immunophenotype+dependent+upon+irradiated+site&journal=Int+J+Radiat+Oncol+Biol+Phys.&volume=101&pages=1259-70)