Göteborg, 2022

The Use of Immunological Biomarkers to Improve Individualization of Postoperative Radiotherapy in Breast Cancer

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Waldemar Sjölander, Medicinaregatan 7A, oktober 21, klockan 09.00.
av Axel Stenmark Tullberg

Fakultetsopponent:
Per Hall, Professor
Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten

I. Kovacs, A., Stenmark Tullberg, A., Werner Rönnerman, E., Holmberg, E., Hartman, L., Sjöström, M., Lundstedt, D., Malmström, P., M. Fernö, and Karlsson, P., Effect of Radiotherapy After Breast-Conserving Surgery Depending on the Presence of Tumor-Infiltrating Lymphocytes: A Long-Term Follow-Up of the SweBCG91RT Randomized Trial.
J Clin Oncol, 2019. 37(14): p. 1179-1187.

II. Stenmark Tullberg, A., Puttonen, H.A.J., Sjöström, M., Holmberg, E., Chang, S.L., Feng, F.Y., Speers, C., Pierce, L.J., Lundstedt, D., Killander, F., Niméus, E., Kovács, A., and Karlsson, P., Immune Infiltrate in the Primary Tumor Predicts Effect of Adjuvant Radiotherapy in Breast Cancer; Results from the Randomized SweBCG91RT Trial.
Clin Cancer Res, 2021. 27(3): p. 749-758.

III. Stenmark Tullberg, A., Sjöström, M., Niméus, E., Killander, F., Chang, S.L., Feng, F.Y., Speers, C., Pierce, L.J., Kovács, A., Lundstedt, D., Holmberg, E., and Karlsson, P., Integrating tumor-intrinsic and immunological factors to identify immunogenic breast cancers from a low-risk cohort- results from the randomized SweBCG91RT trial
Manuscript

IV. Stenmark Tullberg, A., Sjöström, M., Tran, L., Niméus, E., Killander, F., Kovács, A., Lundstedt, D., Holmberg, E., and Karlsson, P., Risk of local recurrence and benefit from radiotherapy based on integrated assessments of histological grade, TILs, PD-1, and PD-L1- results from the randomized SweBCG91RT trial
Manuscript

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UNIVERSITY OF GOTHENBURG

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The Use of Immunological Biomarkers to Improve Individualization of Postoperative Radiotherapy in Breast Cancer

Axel Stenmark Tullberg

Avdelningen för Onkologi, Institutionen för Kliniska Vetenskaper, Sahlgrenska akademin, Göteborgs universitet, Sverige, 22.

Abstract

Radiotherapy (RT) forms the cornerstone of most curative breast cancer treatment due to its well-established risk-reducing effect on local recurrences at the population level. However, there is heterogeneity regarding treatment benefits at the individual level, and research currently aims to better tailor treatment decisions based on tumor biology. This thesis aimed to investigate if immunological biomarkers from the primary tumor can be used to predict the benefit from radiotherapy (RT) at the individual level and improve treatment individualization.

Tumor blocks were collected from the randomized SweBCG91RT cohort. Immunohistochemical and gene expression analyses of immunological biomarkers in the primary tumor were used to study if the benefit from RT could be predicted. An activated immune response was associated with a reduced risk of local recurrence and a reduced need for postoperative RT. The biological implications of an activated immune response depended on tumor-intrinsic characteristics. By integrating these two dimensions, tumors could be identified where a local immune infiltrate's risk-reducing effect was comparable to that obtained from RT.

Immunological biomarkers from the primary tumor provide independent information on the risk of local recurrence, which can be used to stratify patients according to the need for postoperative radiotherapy. An immune infiltrate's implications depend on tumor-intrinsic characteristics, and successful implementation of immunological biomarkers in clinical practice, therefore, requires a co-analysis of such factors. Tumors with an activated immune response may have a low risk of local recurrence and constitute a group where de-escalation of RT may be feasible.

Keywords: Tumor-infiltrating lymphocytes, CD8 T cells, FOXP3 T regulatory cells, radiotherapy, local recurrence, tumor-intrinsic characteristics

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