

Melanoma surgery in the era of modern immunotherapy

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i lokal Hjärtat, Sahlgrenska Universitetssjukhuset, den 23:e februari 2024, klockan 09:00.

av Carl-Jacob Khailat Holmberg

Fakultetsopponent:

Lisbet Rosenkrantz Hølmich, professor

Institut for klinisk medicin, Köpenhamns universitet, Köpenhamn, Danmark

Avhandlingen baseras på följande delarbeten

- I. Holmberg CJ, Ny L, Hieken TJ, Block MS, Carr MJ, Sondak VK, Örtenwall C, Katsarelis D, Dimitriou F, Menzies AM, Saw RP, Rogiers A, Straker RJ 3rd, Karakousis G, Applewaite R, Pallan L, Han D, Vetto JT, Gyorki DE, Tie EN, Vitale MG, Ascierto PA, Dummer R, Cohen J, Hui JY, Schachter J, Asher N, Helgadottir H, Chai H, Kroon H, Coventry B, Rothermel LD, Sun J, Carlino MS, Duncan Z, Broman K, Weber J, Lee AY, Berman RS, Teras J, Ollila DW, Long GV, Zager JS, van Akkooi A, Olofsson Bagge R. **The efficacy of immune checkpoint blockade for melanoma in-transit with or without nodal metastases - A multicenter cohort study.** Eur J Cancer. 2022 Jul; 169:210-222.
- II. Holmberg CJ, Mattsson J, Olofsson Bagge R. **Effects of the introduction of modern immunotherapy on the outcome of isolated limb perfusion for melanoma in-transit metastases.** Cancers (Basel). 2023 Jan; 15(2):472.
- III. Holmberg CJ, Mikiver R, Isaksson K, Ingvar C, Moncrieff M, Nielsen K, Ny L, Lyth J, Olofsson Bagge R. **Prognostic significance of sentinel lymph node status in thick primary melanomas (> 4 mm).** Ann Surg Oncol. 2023 Aug; 30(13):8026–8033.
- IV. Holmberg CJ, Zijlker L, Katsarelis D, Huibers A, Wouters WJM, Schrage Y, Reijers S, van Thienen H, Grünhagen DJ, Martner A, Nilsson J A, van Akkooi ACJ, Ny L, van Houdt W J, Olofsson Bagge R. **The effect of a single dose of nivolumab prior to isolated limb perfusion for patients with in-transit melanoma metastases: an interim analysis of a phase Ib/II randomized double-blind placebo-controlled trial (NivoILP trial).** Submitted manuscript.

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER**



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Carl-Jacob Khailat Holmberg

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Abstract

Recent advances in immuno-oncology have led to a paradigm shift in the treatment of advanced cutaneous melanoma. The aim of this thesis is to investigate the role of surgery in the management of melanoma in this modern era of effective systemic treatments. This is done using a comprehensive approach of both retrospective and prospective study designs. In *Paper I*, we gathered international data from a large number of melanoma centers to examine the efficacy of immunotherapy on melanoma in-transit metastases and found immunotherapy to be effective in this patient group. In *Paper II*, we investigated the effect of isolated limb perfusion in patients that had received previous systemic immunotherapy and found it remains an effective treatment option. In *Paper III*, we used data from the Swedish national melanoma registry to show the prognostic value of sentinel lymph node status also in thick (>4.0 mm) melanomas, and our study supports a recommendation for sentinel lymph node biopsy also for thick tumors. In *Paper IV*, we performed a randomized controlled trial investigating the safety and preliminary efficacy of a single dose of the PD-1 inhibitor nivolumab prior to isolated limb perfusion for in-transit metastases, and found it to be safe and with promising efficacy.

This thesis shows a strong continued role for surgery and locoregional treatments for patients with advanced melanoma, and underscores the evolving and dynamic nature of melanoma management, where a multidimensional approach holds the key to optimizing patient outcomes.

Keywords: melanoma, surgery, immunotherapy, isolated limb perfusion