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Estimation of long-term risks for cancer induction following adjuvant targeted alpha therapy with curative intent.

Risks for induction of secondary cancers following radiation or other therapies of advanced cancers are typically not considered since the estimated life-span of these patients is relatively short. This is often the case for patients currently considered for targeted alpha therapy, TAT. However, TAT may hold most promise as an adjuvant therapy following surgery and/or chemotherapy. It will then be delivered to patients possibly already cured by the primary treatment. In this setting, or for any TAT with curative intent, some estimate of long-term risks is therefore needed for an informed decision whether to justify the treatment.

Within the overall aim to base a decision on justification for adjuvant TAT on a sound risk-benefit evaluation, the specific aim of the current work was to translate the, for intraperitoneal TAT, most relevant data on excess cancer induction and mortality to an estimate of what can be expected following adjuvant intraperitoneal TAT.

Methods
A survey of baseline data for risk estimates of alpha-particle irradiation of organs of interest for intraperitoneal TAT was performed. The well-known studies on excess cancer induction and mortality for subjects exposed to either high-dose-rate 224Ra treatment or Thorotrast contrast agent were selected. Dosimetry have been presented for both 224Ra (1) and Thorotrast (2,3). Organ-specific risks from these studies were then applied on our previously reported dosimetry for intraperitoneal TAT patients (4).

Results
We have previously reported that an infusate concentration of 200 MBq/L 211At-mAb would result in 2.6 Sv effective dose (4). This result indicates a life-long lethal cancer risk of around 10%. When directly translating the results from the 224Ra and Thorotrast studies, this risk is reduced. The organs at highest risk for secondary cancer were the kidneys and lungs, which warrants evaluation of the microscopic distribution of the alpha decays even if secondary cancers in these organs have relatively long latency. For intraperitoneal TAT, the risk for hematological malignancies seems very low.

Conclusion
There are obvious and large uncertainties in both excess cancer incidence and dosimetry. Overall, however, the results indicate that some estimate of long-term risk for cancer induction can be derived. For TAT, such data are seldom used, but could strengthen a risk-benefit analysis of use in patient selection and dose optimizations of TAT with curative intent.

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