Comparison of subcutaneous and orthotopic tumor growth in syngeneic mouse models of ovarian and renal cancer

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Introduction

Oncology drug development has markedly lower success rate (3.4%) than other indications (20.9%) as reported by Wong, Siah and Lo in 2019. Animal models are often pointed at as the culprits for failure in clinical trials. While better animal models for cancer are needed and constantly developed, the incentive of drug developers to use those might not be clear, because the regulatory authorities do not require it. Subcutaneous tumors have earned their place in drug development but adding more sophisticated models to the testing panel before entering the clinical phase should improve the success rate.

Aim of the Study

The aim was to compare the properties of subcutaneous and orthotopic tumor growth in two syngeneic models.

Materials and Methods

HM-1 murine ovarian cancer cells (RIKEN BioResource Research Center, Japan) were inoculated subcutaneously (s.c.) and intraperitoneally (10^6 cells), representing the stage of intraperitoneal carcinomatosis, to 5-week-old female B6C3F1/OlaHsd mice (Envigo), and murine renal adenocarcinoma RENCA cells (ATCC) s.c. ($5x10^5$ cells) and orthotopically within the renal capsule (10^5 cells) to 5-6 weeks old female Balb/c mice. Body weight and tumor growth were followed, and mice were sacrificed according to humane endpoint criteria. To compare tumor growth in s.c. sites and within the abdomen, the tumor weight at sacrifice was divided by the number of days since the inoculation.

Body weight

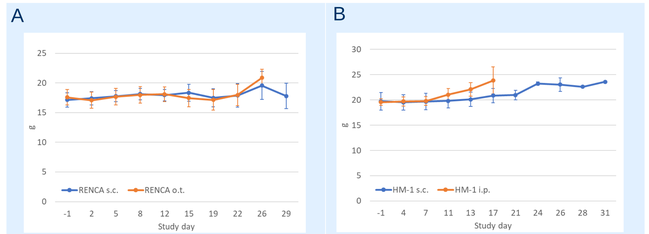


FIGURE 1. Body weight (g, mean ± SD). A) RENCA tumor bearing mice. B) HM-1 tumor bearing mice.

Survival

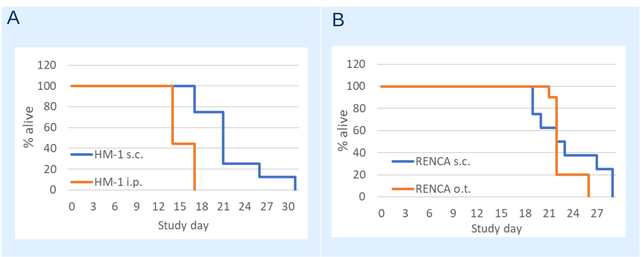
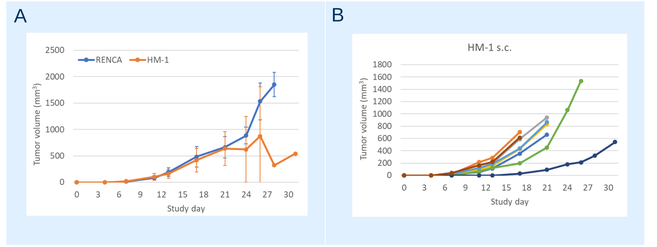


FIGURE 2. Survival in the subcutaneous vs intraperitoneal/orthotopic A) HM-1 and B) RENCA models. In the HM-1 model, the mice with intraperitoneal tumor were sacrificed due to build-up of ascites on average six days earlier that the mice with s.c. tumor. S.c. tumor ulceration was observed in all HM-1 tumors and in 5/8 RENCA tumors.

Tumor growth s.c.



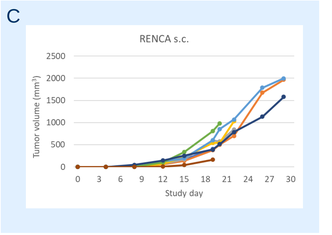


FIGURE 3. The growth of s.c. tumors (mm^3).
A) Mean ± SD of HM-1 and RENCA tumors.
B) Individual HM-1 tumors
C) Individual RENCA tumors

S.c. vs intraperitoneal/orthotopic growth

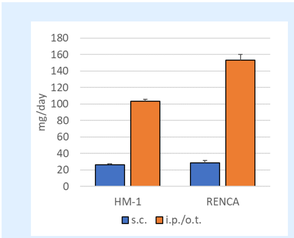


FIGURE 4. The mean growth (±SD, mg/day) of tumors at subcutaneous, intraperitoneal and orthotopic sites. The parameter was calculated by dividing the weight of each tumor by the sacrifice day.
There was a striking difference in the tumor growth rate (mg/day) in s.c. versus abdominal sites in both models. The growth was 4 times faster in the intraperitoneal than subcutaneous site in the HM-1 model, and 5 times faster in the intrabursal site compared to the s.c. site. The difference highlights the effect of tumor specific microenvironment on tumor growth rate.

Summary

- In the HM-1 model, the mice with intraperitoneal tumor were sacrificed on average six days earlier that the mice with s.c. tumor.
- In s.c. HM-1 tumor-bearing mice, the reason for sacrifice was tumor ulceration.
- In s.c. RENCA tumor-bearing mice, the reason for sacrifice was tumor ulceration in 5/8 mice.
- In the RENCA model, the s.c. and intrabursal models were approximately the same length.
- Intraperitoneal or intrabursal growth was 4-5 times faster than s.c. growth.

Conclusions

- Markedly higher tumor growth rate (mg/day) in s.c. versus abdominal sites in both models.
- The growth was 4-5 times faster in the abdominal than subcutaneous sites, highlighting the effect of tumor specific microenvironment.
- Testing drug candidates in a relevant site before accessing the clinical trials could give a more accurate evaluation of the potency of the drug candidates.

References

Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019 Apr 1;20(2):273-286. doi: 10.1093/biostatistics/kxx069. Erratum in: Biostatistics. 2019 Apr 1;20(2):366. PMID: 29394327; PMCID: PMC6409418.

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