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## **Incidental detection of malignancy during pre-procedural workup for transcatheter aortic valve implantation: a longitudinal cohort study**

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**Brief title:** Incidental findings detected during TAVI workup

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**One sentence summary:** “Incidental malignancy is detected in 4.5% of patients undergoing workup for TAVI, and is associated with adverse five-year outcome.”

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**ABSTRACT**

The aim of this retrospective analysis was to investigate the prevalence and prognostic importance of incidental malignancy detected during pre-TAVI computed tomography.

Among 579 patients, CT-work-up for TAVI exposed previously undetected malignancy in 4.5% of patients. TAVI patients with a new malignancy had a 2.9-fold increased risk of death at one year, and a 16 month shorter mean survival time compared to patients with no malignancy.

**Keywords:** transcatheter aortic valve implantation, TAVI, computed tomography, CT, incidental findings, malignancy, cancer, survival

## **Introduction**

Transcatheter aortic valve implantation (TAVI) requires meticulous pre-procedural planning. Computed tomography (CT) of the thorax, abdomen and pelvis constitutes a cornerstone in the evaluation of anatomic feasibility and suitability for TAVI. As a collateral effect of comprehensive imaging, incidental findings can be detected during pre-TAVI workup. Previous studies reported clinically relevant incidental findings in up to half of all patients under evaluation for TAVI, but failed to quantify the prognostic relevance of these findings.<sup>1, 2</sup> Malignancy is the most relevant incidental finding and can importantly alter further clinical management and prognosis. The aim of the present study was to investigate the prevalence and prognostic importance of incidental malignancy detected during pre-TAVI CT.

## **Methods**

### **Study design and population**

The study was based on a prospectively collected data from an ongoing registry, which includes consecutive patients undergoing TAVI for severe, symptomatic aortic

stenosis at Bern University Hospital in Switzerland. Details of the Bern TAVI registry have been reported previously<sup>3</sup>. The study has been approved by the local ethics committee and all patients provided written informed consent for participation. For the purpose of the present study, all patients undergoing TAVI between January 2015 and December 2016 and undergoing pre-procedural CT were considered. Patients with known malignancy and patients with procedural death were excluded. No extramural funding was used to support this work.

#### **Data collection and Definitions**

Data on incidental findings were retrospectively identified by systematic review of radiological reports of all TAVI CTs performed during the study period. Incidental findings were further evaluated if suspicious for malignancy, and the diagnosis of malignancy was verified by histopathology reports, tumor markers, or specific radiological tests. Incidental radiographic findings were categorized according to the organ system. Data on clinical management of malignancy was retrieved from discharge summaries. Standardized clinical follow-up was prospectively collected at 30 days, 1 year and 5 years after TAVI as previously described.<sup>3</sup>

## Statistical analysis

Categorical variables are reported as frequencies and percentages. Continuous variables are presented as mean values  $\pm$  standard deviation (SD). Cumulative event curves were calculated using the Kaplan-Meier method and hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox proportional hazards models. We performed a restricted mean survival time (RMST) analysis because it provides an integrated patient-oriented measure of the expected event-free survival time and is less liable to violations of the proportional hazards assumption.<sup>4</sup> RMST was estimated from the non-parametric integration of the area under the Kaplan-Meier curves. All p-values were two-sided, and a p-value  $< 0.05$  was considered significant for all tests. All statistical analyses were performed with Stata 15.1 (StataCorp, College Station, TX, USA).

## Results

Among 579 patients undergoing CT prior to TAVI between January 2015 and December 2016, 575 were included in the present study. Incidental findings were reported in 365 patients (63.5%). Malignancy was suspected in 116 patients (20.2%) and confirmed in 26 patients (4.5%) (**Figure 1**). Among patients with incidental

malignancy, cancer staging was available in 11 patients (stage I/II: 7 and stage III/IV: 4), while 15 patients refused further investigations for the purpose of staging of disease.

Patient with incidental malignancies detected during pre-evaluation for TAVI were comparable to patients with no malignancy with regards to age ( $81.0 \pm 6.6$  years versus  $81.6 \pm 6.7$  years,  $p = 0.703$ ), sex (females 46.2% versus 50.6%,  $p = 0.692$ ), and cardiovascular comorbidities. Malignancy was most commonly found in the lung 7 (27%) and the urogenital system 7 (27%) followed by the gastrointestinal system 3 (16%). Sixteen patients (61.5%) declined oncological therapy, while 10 patients underwent treatment (chemotherapy  $n = 9$ , radiation therapy  $n = 4$ , or tumor surgery  $n = 5$ ).

Clinical follow-up was complete in 96.2% of patients at 5 years. Among 26 patients with incidental malignancy, 18 patients died during the study period (cancer-related death 12; cardiovascular death 5; and unknown 1). All cause death was significantly higher in patients with malignancy compared with those without malignancy at one year (31.9% versus 11.4%, HR 2.87, 95% CI 1.37-6.00,  $p = 0.005$ ) and at 5 years (72.0% versus 43.4%, HR 2.48, 95% CI 1.54-4.02,  $p < 0.001$ ) (**Figure 2**).

The RMST of patients with incidentally detected malignancy was 488 days (95% CI 216-759) shorter compared to patients with no malignancy.

## Discussion

The salient findings of this study can be summarized as follows. First, incidental malignancy was detected in 4.5% of patients during pre-evaluation for TAVI. Second, almost one third of patients with incidentally detected malignancy during pre-TAVI CT died within 1 year after TAVI. The risk of death within 1-year after TAVI was 2.9 times increased compared to patients with no malignancy, and the restricted mean survival time after TAVI was 16 months shorter compared to patients with no malignancy.

In the present study, the observed prevalence of incidental findings, significant incidental findings, and incidental malignancy was 63.5%, 20.2%, and 4.3%, respectively, which is consistent with previous reports<sup>1, 2, 5</sup>. Notably, less than one in ten patients with an incidental finding was eventually diagnosed with malignancy. Several studies have investigated the clinical impact of incidental findings. A recent meta-analysis concluded that significant incidental findings, defined as an incidental finding

that was potentially pathological and required further investigation or treatment prior to TAVI, were not associated with mortality up to 3 years, but were associated with an increased risk of mortality when evaluated at  $\geq 4$  years<sup>5</sup>. In the present study, we observed that a new diagnosis of malignancy during pre-TAVI work-up had an important impact on prognosis that materialized already within the first year after TAVI. Our findings are consistent with a previous report that examined the clinical impact of active cancer in patients undergoing TAVI. In the latter study, patients with cancer had a more than twofold increased mortality after TAVI compared with those without cancer (HR: 2.37, 95% CI: 1.74-3.23)<sup>6</sup>. Our results suggest that incidentally detected malignancy may be the main driver of adverse outcome in patients with incidental findings during TAVI work-up while other incidental findings may be less prognostically relevant.

Current guidelines recommend the review and reporting of incidental findings, as the importance of incidental findings will increase as the life expectancy of patients undergoing TAVI increases<sup>7,8</sup>. Incidental detection of malignancy conceptually allows for an earlier diagnosis and timely treatment that may result in a favorable prognosis for

the individual patient. On the downside, work up of potential malignancy leads to significant costs, patient anxiety, and arguably delays in TAVI. The latter may directly interfere with prognosis, and is of particular concern given the overdiagnosis of incidental findings suspicious of malignancy. In contrast, incidental detection of malignancy allows for an earlier diagnosis and timely treatment that may result in a favorable prognosis for the individual patient. Indeed, previous studies have reported that there is no delay in time to TAVI in patients with significant incidental findings<sup>5</sup>.

The diagnosis of incidental malignancy during TAVI work-up requires an individualized treatment strategy and a shared-decision making process. TAVI is considered futile in patients with a life expectancy of less than one year.<sup>9</sup> Weighting the probabilities of cardiac versus cancer-related death is however often challenging. At the same time, TAVI may be warranted for symptom relief, and may reduce the risk of cancer treatment. Indeed, 40% of patients with incidental malignancy underwent oncological therapy after TAVI in the present study. Further studies are needed to evaluate the prognostic effect of oncological treatment following TAVI in patients with incidental malignancy, especially in younger population.

## Limitation

The findings of the present analysis should be interpreted in light of several limitations. First, the present study includes only patients that underwent TAVI. Patients that did not undergo TAVI after a new diagnosis of malignancy are not reflected in the present registry. The reported prevalence of incidental malignancy may therefore be underestimated. Second, the study reports on patients undergoing TAVI in 2015 and 2016. Consequently, elderly patients with significant comorbidities were included. The reported prevalence may therefore not be generalizable to younger patients at lower risk. Third, even though clinical events were independently adjudicated, the number of cases with incidental malignancy was relatively small. Therefore, it is difficult to interpret the significance of cancer contributing to death and we cannot differentiate direct mortality from cancer from mortality associated with treatment of cancer. Finally, we could not determine the cancer staging in all patients with incidental malignancy. The higher mortality in patients with incidental malignancy may be overestimated by the presence of patients at the advance cancer stage (stage III/IV), who have a life expectancy of less

than one year. Patients with advanced stages of cancer may have been referred to TAVI rather than surgery.

### **Conclusion**

In conclusion, CT-work-up for TAVI exposed previously undetected malignancy in 4.5% of patients. TAVI patients with a new malignancy had a 2.9-fold increased risk of death at one year, and a 16 month shorter mean survival time compared to patients with no malignancy.

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organizations. In particular, pharmaceutical and medical device companies provide direct funding to some of these studies. For an up-to-date list of CTU Bern's conflicts of interest see [http://www.ctu.unibe.ch/research/declaration\\_of\\_interest/index\\_eng.html](http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html). All other authors have no relationships relevant to the contents of this article to disclose.

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## References

1. Patel A, Mahendran K, Collins M, Abdelaziz M, Khogali S, Luckraz H. Incidental abnormal CT scan findings during transcatheter aortic valve implantation assessment: incidence and implications. *Open heart* 2018;5(2):e000855.
2. Showkathali R, Sen A, Brickham B, Dworakowski R, Wendler O, MacCarthy P. "Incidental findings" during TAVI work-up: more than just an inconvenience. *EuroIntervention* 2015;11(4):465-9.
3. Okuno T, Demirel C, Tomii D, Heg D, Haner J, Siontis GCM, et al. Long-term risk of unplanned percutaneous coronary intervention after transcatheter aortic valve replacement. *EuroIntervention* 2022;18(10):797-803.
4. Royston P, Parmar MK. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol* 2013;13:152.
5. Ko K, Zwetsloot PP, Voskuil M, Stella P, Leiner T, Kraaijeveld A. Clinically Significant Incidental Findings on CT Imaging During TAVI Work-up: A Systematic Review and Meta-Analysis. *J Invasive Cardiol* 2022;34(3):E218-e225.
6. Landes U, Iakobishvili Z, Vronsky D, Zusman O, Barsheshet A, Jaffe R, et al. Transcatheter Aortic Valve Replacement in Oncology Patients With Severe Aortic Stenosis. *JACC Cardiovasc Interv* 2019;12(1):78-86.
7. Blanke P, Weir-McCall JR, Achenbach S, Delgado V, Hausleiter J, Jilaihawi H, et al. Computed Tomography Imaging in the Context of Transcatheter Aortic Valve Implantation (TAVI)/Transcatheter Aortic Valve Replacement (TAVR): An Expert Consensus Document of the Society of Cardiovascular Computed Tomography. *JACC Cardiovasc Imaging* 2019;12(1):1-24.
8. Francone M, Budde RPJ, Bremerich J, Dacher JN, Loewe C, Wolf F, et al. CT and MR imaging prior to transcatheter aortic valve implantation: standardisation of scanning protocols, measurements and reporting-a consensus document by the European Society of Cardiovascular Radiology (ESCR). *Eur Radiol* 2020;30(5):2627-2650..
9. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al.

2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022;43(7):561-632.

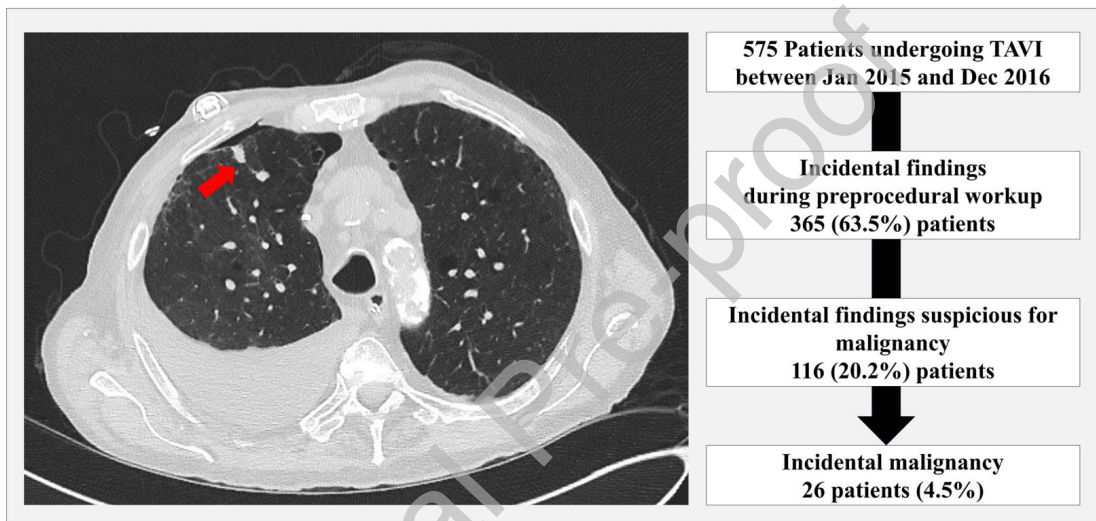
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### Figure Legends

#### Figure 1. Study flowchart

Study flowchart and sample case showing incidental findings on preprocedural computed tomography (**Red arrow**).

TAVI = transcatheter aortic valve implantation.



**Figure 2. Kaplan-Meier curves for all- cause death**

Hazard ratios and p-values were calculated with the use of Cox proportional hazards models.

TAVI = transcatheter aortic valve implantation.

