Earlier Recurrence Detection Using Routine FDG PET-CT Scans in Surveillance of Stage IIB to IIID Melanoma

A National Cohort Study of 1480 Patients

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Earlier recurrence detection using routine FDG PET-CT scans in surveillance of stage IIB-IIID melanoma: A national cohort study of 1,480 patients.

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Synopsis

This prospective national cohort study compared hazard rates of recurrence in melanoma patients followed with and without routine FDG PET-CT scans. Routine FDG PET-CT improved distant recurrence detection with a 51% increase in hazard rate in the first two years.

Abstract

Introduction

The effect of routine imaging in melanoma surveillance is unknown. In 2016, Denmark was the first country in the world to implement routine imaging with positron emission tomography-computed tomography with fluorodeoxyglucose (FDG PET-CT) in a nationwide, population-based surveillance program.

The aim of this study was to determine the impact of surveillance with routine FDG PET-CT on hazard, cumulative incidence, and absolute risk of overall, locoregional, and distant recurrence detection in stage IIB-IIID cutaneous melanoma patients.

Methods

This retrospective, population-based, nationwide cohort study used prospectively collected data from five national health registries to compare hazard, cumulative incidence, and absolute risk of recurrence in patients diagnosed in 2008-2010 (cohort 1, followed with clinical examinations) and patients diagnosed in 2016-2017 (cohort 2, followed with clinical examinations and routine FDG PET-CT at 6, 12, 24, and 36 months).

Results

1,480 stage IIB-IIID patients were included. Cumulative incidences of recurrence and distant recurrence were higher in cohort 2 with a peak difference around three years (32.3% vs. 27.5% and 25.8% vs. 18.5%, respectively). Hazard of recurrence was higher in cohort 2 for the first two years, with hazard rates of overall and distant recurrence of 1.16

(95% CI: 0.93 - 1.44) and 1.51 (95% CI: 1.16 - 1.96). Patterns persisted in absolute risk estimates.

Conclusions

Stage IIB-IIID melanoma patients followed with routine FDG PET-CT had a 51% increased hazard of distant recurrence detection within the first two years of surveillance. Future studies must determine whether this earlier recurrence detection will translate into improved survival.

Introduction

To ensure early recurrence detection in melanoma, patients are followed in stage-specific risk-stratified surveillance programs[1–5]. International protocols differ significantly, and a major point of controversy is the use of routine imaging in surveillance. Most programs recommend the consideration[1,2], or use[3,5], of routine cross-sectional imaging in high-risk patients, but there is no consensus regarding recommended imaging modality, frequency, duration, or to which patients it should be offered.

In 2016, Denmark was the first country in the world to implement routine imaging with positron emission tomography-computed tomography with fluorodeoxyglucose (FDG PET-CT) to a nationwide surveillance program[4]. An early evaluation of the program showed that routine FDG PET-CT detected recurrence in 17.1 % of patients, including occult distant recurrence in 13.8%, within a median follow-up of 17.7 months[6]. Retrospective observational studies have reported the yield of other routine imaging schedules[7–10] but the impact of routine imaging on recurrence detection has yet to be described in a comparative analysis.

This study aimed to investigate the impact of surveillance with routine FDG PET-CT on hazard, cumulative incidence, and absolute risk of overall, locoregional, and distant recurrence detection in stage IIB-IIID cutaneous melanoma patients.

Methods

Study design

This is a retrospective study of prospectively collected data from two consecutive nationwide population-based cohorts of Danish stage IIB-IIID melanoma patients followed with and without routine FDG PET-CT.

Study context and procedures

In Denmark, melanoma patients are followed in a national stage-specific, risk-stratified program. Per January 1st, 2016, routine whole-body FDG PET-CT at 6, 12, 24, and 36 months were added to the surveillance-program for stage IIB-IIID patients (**Figure 1**).

In all centers but one, whole-body FDG PET-CT is obtained with low-dose CT from base of scull to mid-thigh, with inclusion of extremities if relevant to primary tumor localization. In the last center, where approximately 18% of patients are followed[11], FDG-PET CT is performed using diagnostic dose CT with iv contrast.

Primary treatment was unchanged throughout the study period; in Denmark,T1 melanomas are operated with a 1 cm resection margin and thicker tumors with 2 cm resection margin; if localizations allows (fulfilled in 96-97% of cases in 2016-2017[12,13]). All T1b+ patients were offered sentinel node (SN) biopsy, unless comorbidity contraindicated the procedure (performed in 77-80% of T1b+ patients in 2016-2017[12,13]). Completion lymph node dissection (CLND) was performed routinely in case of SN metastases during this period. As adjuvant therapy was not implemented until early 2018, no patients in this study received adjuvant therapy at time of primary treatment.

Participants

Patients were included based on their prospective registration in the Danish Melanoma Database (DMD)[14]. We included all American Joint Commission of Cancer Eighth Edition Cancer Staging Manual (AJCC8) stage IIB-IIID patients ≥18 years diagnosed and treated for first-time stage IIB-IIID melanoma in 2008-2010 (cohort 1) and in 2016-2017 (cohort 2). Patients in cohort 1 were followed with clinical examinations alone but had access to cross-sectional imaging with FDG PET-CT (in smaller centers computed tomography (CT)), upon suspicion of recurrence. Patients in cohort 2 were followed with clinical examinations and whole-body routine FDG PET-CT at 6, 12, 24, and 36 months and were further referred to FDG PET-CT if recurrence was suspected between routine scans. In case of synchronous melanomas, patients were included with data from the melanoma of highest pathological stage. Patients were excluded if no pathology report corresponding to the primary tumor was found in the Danish Pathology Register (DPR)[15].

The risk of selection bias was deemed low and warranted no alterations to patient inclusion or study design.

Outcomes

The primary outcome of this study was the effect of surveillance with routine FDG PET-CT on the hazard of overall, locoregional and distant recurrence.

Secondary outcomes were differences in estimated cumulative incidence and absolute risk of overall, locoregional and distant recurrence at six months and one, two, three, and five

years for patients followed with routine FDG PET-CT compared to patients followed with clinical examinations only.

Data sources and key variables

This study used prospectively collected data from the DMD[14], the DPR[15], the Danish National Patient Register (NPR)[16], the Danish Civil Registration System (CPR)[17], and the Danish Cause of Death Registry (DAR)[18].

The DMD was established in 1985 and has since 2013 been in function as a national clinical quality database, to which all Danish melanoma patients are prospectively registered with information regarding primary treatment, surveillance, and recurrence[14]. Data have been validated from 2000 and onwards and are annually validated against the DPR, which contains nationwide data on all pathological specimens evaluated in Denmark since 1997[15] (data coverage 94-95% in 2019-2021[11]). Patients are further registered to the NPR, which contains nationwide data on all in-hospital patient contacts since 1977 and all out-hospital patient contacts since 1995, including diagnostic codes, treatments, and investigations[16]. The CPR was established in 1968 and is the Danish civil registration system, where all residents are registered with a unique 10-digit personal identification number (CPR-number). The CPR contains data regarding vital- and emigration-status and is updated on a daily basis. In register-based health research, the CPR-number is used as the key variable enabling linkages between data sources. The CPR is further used for validation of other registries, including the DAR, which contains data regarding causes of death in Denmark with national coverage since 1977[17,18].

In this study, tumor and patient characteristics (age, sex, pathological subtype, ICD-10 localization, TNM-stage, date of final primary treatment and AJCC8 pathological stage were obtained from the DMD. AJCC8 TNM-stages were calculated for all patients using DMD- and DPR-data with relevant assumptions in cases of missing data, as descried in a previous study (Helvind et al., unpublished data). Charlson's Comorbidity Index (CCI)[19] was estimated based on hospitalization diagnoses registered in the NPR ten years prior to the date of the primary melanoma diagnosis and was categorized as low (CCI=0), medium (CCI=1-2), or high (CCI>2). Recurrence data were obtained from the DMD and supplemented with data from the DPR and the NPR, as described in a previous study (Helvind et al., unpublished data). We extracted the date of first locoregional, distant and unclassifiable recurrence registered at least 90 days after finalized primary treatment for analyses; this time-limit was chosen to avoid misclassification of staging records as recurrences in the recurrence algorithm. Recurrence was categorized as unclassifiable if localization information did not allow for distinguishing between recurrence types.

Mortality data, including vital status and cause of death were included from the CPR and the DAR.

Data regarding emigration or development of a new primary melanoma of higher AJCC8 stage were included from the CPR and DMD

Statistical Analyses

Descriptive data for each cohort were reported as mean with 95% confidence interval (95%CI) if approximately normally distributed, or as median with interquartile range (IQR),

if not. Data were compared using χ^2-test for categorical data or student's t-test for continuous variables with statistical significance at the 95% level.

We used year of primary diagnosis (cohort) as a proxy for surveillance program employed. To determine the impact of surveillance with routine FDG PET-CT on recurrence detection, cumulative incidences of overall, locoregional, and distant recurrence at six months and one, two, three, and five years after primary treatment were estimated for each cohort using the Aalen-Johansen estimator,[20] with recurrence as primary event and death before recurrence (death from all causes) as a competing event.

Patients were followed until recurrence, death or end of follow-up on December 31st, 2021 and censored in the event of emigration (loss-to-follow-up) or development of a new primary melanoma of a higher AJCC8 pathological stage.

To determine the cohort effect on the hazard of recurrence, cause-specific proportional hazards-models (CSH) for overall, locoregional, and distant recurrence were fitted and HR with corresponding 95% CI estimated comparing cohort 2 with cohort 1.

Potential confounders included in CSH-models were age, sex, CCI, histopathological subtype of melanoma (superficial spreading, nodular, lentigo maligna, acrolentiginous, desmoplastic, and unclassifiable melanoma), and ICD-10 localization of primary tumor (head and neck, trunk, upper or lower extremities, genitalia, or unknown).

The proportional hazards assumption for CSH-models was tested by graphical evaluation of the scaled Schoenfeld residual plots for any trends. If the assumption of proportional hazards was violated for the cohort variable, models were fitted for appropriate time periods and HR reported for these and for confounders by using separate baselines for each level of the offending variables. For sub-periods, cohort- and stage-specific absolute

risk (AR) of overall, locoregional and distant recurrence were estimated based on CSH models.

All outcomes were presented with corresponding cumulative incidences, HR, and AR for competing event (death from all causes before overall, locoregional and distant recurrence, respectively).

Data were analyzed using R Statistical Software (v4.1.3)[21] and all analyses performed in collaboration with a senior biostatistician.

Results

A total of 1,480 stage IIB-IIID patients were included for analysis; 765 patients in cohort 1 and 715 patients in cohort 2 (**Figure S1)**. Patients were followed for a median of 10.8 and 4.5 years in cohort 1 and 2, respectively. There was a higher proportion of male patients and patients of higher age and comorbidity index in cohort 2 and a higher proportion of patients with nodular melanoma (NM) in cohort 1 (**Table 1)**.

The cumulative incidence of overall recurrence was higher in cohort 2 compared to cohort 1; the difference appeared greatest for the first two to three years following primary treatment (3-year rates 27.5% vs. 32.3% for cohort 1 and cohort 2, respectively), whereafter rates began to converge. The difference was less pronounced for locoregional recurrence and more pronounced for distant recurrence (18.5% vs. 25.8% at three years). The cumulative incidence of the competing event, death before recurrence, was higher in cohort 2 (**Figures 2-4** and **Table 2).**

Model-testing of CSH-models showed violation of the proportional hazards assumption with a higher hazard of recurrence in cohort 2 for the first 1-2 years (**Figure S2**, supplementary material). A time cut for sub analyses was set at two years based on graphical evaluation and consideration of timing of routine FDG PET-CT in the surveillance program.

Within the first two years of surveillance, patients in cohort 2 had a higher hazard of distant recurrence and a tendency towards higher hazard of overall recurrence compared to patients in cohort 1 (HR 1.51 (95% CI: 1.16-1.96) and 1.19 (95% CI: 0.93 - 1.44), respectively), while the hazard of locoregional recurrence was comparable between cohorts. After two years, the hazard of overall, locoregional, and distant recurrence was lower for cohort 2. For all models, the hazard of death before recurrence was comparable between cohorts for the first two years, after which the hazard was higher in cohort 2 for the remaining study period. At two years, we found higher AR of overall, locoregional, and distant recurrence and lower AR of death before recurrence for cohort 2. Results of CSH-analyses are shown in **Table 3**.

Discussion

Though many studies have evaluated the yield of surveillance with different schedules of routine cross-sectional imaging, we believe this to be the first study comparing two uniformly treated, nationwide, and population-based cohorts followed with the same frequency of clinical examinations to determine the impact of added routine FDG PET-CT on recurrence detection. Recurrence detection, and especially distant recurrence detection, was higher in patients followed with routine FGD PET-CT for the first two years of surveillance. We found a 51% increased hazard of distant recurrence detection and a tendency towards higher hazard of overall recurrence detection within the first two years of surveillance for patients followed with clinical examinations and whole-body FDG PET-CT compared to patients followed with clinical examinations alone. As distant recurrences are not as readily detected by clinical examination as locoregional metastases, this confirms our expectations and demonstrates the yield of routine FDG PET-CT in melanoma surveillance.

Recurrence rates

A model-based study of the effect of surveillance with biannual routine CT or FDG PET-CT predicted 5-year distant recurrence rates of 18.5 and 33.1% in stage II-III patients, respectively[22] and a recent Australian retrospective study of patients followed with routine CT or FDG PET-CT reported distant recurrence rate of 33% in stage IIIA-D patients[7]. This corresponds well with our findings of 5-year distant recurrence rates of 29.8% in stage IIB-IIID patients in cohort 2.

Recurrence detection

In this study, surveillance with FDG PET-CT at 6, 12, 24, and 36 months increased distant recurrence-detection with a HR of 1.51 within the first two years of surveillance but did not appear to effect locoregional recurrence detection. This is in line with a recent study of recurrence detection in stage II patients, which found distant recurrences more likely to be detected by imaging and less likely to be clinically detected than locoregional recurrences[23]. Studies of recurrence detection in melanoma are heterogeneous regarding underlying surveillance modalities, which makes a comparison of reported rates difficult. Prior to the introduction of Checkpoint-inhibitor treatments for metastatic melanoma in 2011, patients were rarely followed with routine imaging and, in that setting, recurrences were most frequently detected by patients themselves or their partners (17-72% of first recurrences) or by clinical examination (18-71%)[24,25]. However, the proportion of patients with distant recurrence at time of first recurrence reported in that period was considerably lower than in more recent studies of patients followed with routine imaging (23-28% vs. 49.9-53%)[8,9,24,26,27]. This indicates a gain of routine imaging and increased imaging availability on distant recurrence detection. The proportion of imaging-detected recurrences in patients followed with different schedules of routine CT or FDG PET-CT range from 24.6%-53.9% for stages IIB-III[23,28] and is generally higher in higher stages. For distant recurrence-detection, a recent study of 332 stage III patients found that 78% of asymptomatic distant recurrences were detected by routine CT or FDG PET-CT for patients followed for 5 years with annual or biannual routine scans[7].

Duration and frequency of routine imaging

The benefit of routine FDG PET-CT in stage IIB-IIID melanoma patients was greatest within the first two years of surveillance. This is supported by a recent study of long-term surveillance with CT or FDG PET-CT, which showed decreasing distant recurrence rates across five routine scans performed six or 12 months apart with constant sensitivity, specificity, positive, and negative predictive values of scans over time[7]. A similar trend of decreasing yield over time was found in early results from the Danish surveillance program[6]; however, longer follow-up is needed to evaluate the yield of 24 and 36 month routine scans and to determine the optimal timing and duration of routine imaging in surveillance. Recommended imaging frequency differ across current surveillance guidelines[2,4,5]. In a model-based study of surveillance with biannual or annual routine CT or FDG PET-CT, biannual routine imaging resulted in significantly higher 5-year rates of recurrence detection (18.5% vs. 13.0% for stage II patients and 33.1% vs. 7.9% for stage III patients)[22]. This is in line with results from a recent Australian study of 473 stage IIIA-IIID patients, which found that patents followed with a higher imaging frequency had shorter distant recurrence-free survival and a higher proportion of imaging-detected distant recurrences.

The effect of routine imaging on survival

The ultimate argument in favor of routine imaging in melanoma surveillance would be a proven effect on survival. As distant recurrence carries a significantly poorer prognosis than locoregional recurrence[9,29] and as treatment responses and survival rates may be improved in patients with low metastatic burden and non-elevated LDH and surgically

resectable metastases[30–32], one could speculate that our findings of an early effect of routine FDG PET-CT on distant recurrence detection may translate into improved survival. The few studies that have investigated the effect of routine imaging on survival to date were either limited by study period (i.e., probability models based on data from patients diagnosed from 1992 to 2007, who did not yet have access to modern metastatic treatments if recurrence was detected)[22] or selection bias (i.e., poorer prognostic characteristics in patients receiving high-frequency imaging)[8]. The effect of routine imaging on survival is difficult to investigate in observational studies owing to the risk of selection, lead-time, and length bias. Though the risk of selection bias is minimal when all patients are enrolled in a uniform surveillance protocol such as ours, and lead-time and length bias can be addressed statistically[33], the effect of surveillance with routine imaging on survival should be investigated in a randomized controlled setting. The results of the ongoing Swedish TRIM-trial[34] are awaited.

Strengths and Limitations

A limitation in this study is the differences in patient characteristics between cohorts; patients in cohort 2 were generally older, had a higher comorbidity index, and were more likely to present with NM. This is in line with previously reported time-trends in melanoma in Denmark from 1985 to 2012, which showed a marked increase in the proportion of patients over the age of 60[35]. In the same study, the proportion of NM increased over time, which could explain the higher proportion of NM seen in cohort 2. Consequently, patients in cohort 2 had a higher risk of death before recurrence, which in turn lowered the cumulative incidence of recurrence; if patients had been more comparable, the differences

in recurrence would likely have been greater. Another limitation in this study is the lack of information regarding mode of recurrence detection. As we do not know if recurrences were detected by routine imaging, clinical examination, patient themselves, or by imaging performed on other indications, we cannot say if the increase in recurrence detection was entirely attributable to routine imaging. It seems unlikely that rates of physician- and patient-detected distant recurrence should have increased, however, a general increase in the use of cross-sectional imaging could cause more distant recurrences to be incidentally detected by other imaging investigations than routine FDG PET-CT. Finally, our analyses are limited by the sample size available; owing to alterations in primary treatment in 2018, i.e., the abandonment of routine CLND following the MSLT-II and DeCOG-SLT trials[36,37] and the introduction of adjuvant treatment for stage III patients, we did not include patients diagnosed later than 2017. Though the sample size was sufficiently large to show an effect of routine FDG PET-CT on distant recurrence detection within the first two years of surveillance, significance was not reached for overall recurrence detection in the same period or for distant recurrence detection in individual pathological stages. Given the advantageous prognosis of stage IIIA patients concerning both recurrence (Helvind et al., unpublished data) and mortality [38], it would have been interesting to see if the effect on distant-recurrence detection applies to this stage as well.

A major strength in this study is the nature of our prospectively collected nationwide, population-based data. As all patients in the current study were enrolled in a national surveillance-program and as Danish health-care is tax-funded and freely available to all, the risk of selection bias is minimal. Strict adherence to national treatment and surveillance guidelines, as audited in annual quality reports from the DMD, to which registration is

mandatory, ensures that all patients were treated and followed uniformly, and that data were registered prospectively with excellent data completion and report rates[11].

Conclusion

Routine imaging with whole-body FDG PET-CT at 6, 12, 24, and 36 months increased the hazard of distant recurrence detection by 51% within the first two years of surveillance in stage IIB-IIID patients. Future studies should investigate the optimal timing of routine imaging in different disease stages and randomized clinical trials must determine whether this earlier distant recurrence detection will translate into improved survival.

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Race/ethnicity data

As Danish registries do not register race and ethnicity, we were unable to include this information in the patient characteristics of Table 1.

Permissions

This study was registered and approved by the Danish Health Data Protection Agency (permit no.: P-2019-721).

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Figure legends

Figure 1. The Danish 5-year surveillance program for stage IIB-III melanoma from 2008-2021.

Legend: After conclusion of the 5-year surveillance program, patients are recommended continued annual skin examinations for the subsequent five years. Abbreviations: H&P = Focused patient history and physical examination, including full skin examination with palpation of surgical site, lymphatic drainage and major lymphnode stations. PET-CT = Whole-body scans with positron emission tomography-computed tomography with fluorodeoxyglucose.

Figure 2. Estimated cumulative incidence of recurrence and death before recurrence in melanoma patients followed with and without routine FDG PET-CT scans: Data from 1,480 Danish stage IIB-IIID patients.

Legend: Cumulative incidence of recurrence and death before recurrence in 715 stage IIB-IIID melanoma patients followed with clinical examinations and routine FDG PET-CT (primary diagnosis in 2016-2017) compared to 765 patients followed with clinical examinations alone (primary diagnosis in 2008-2010). Abbreviations: Competing event = death before recurrence, mo = months, yr = year, yrs = years.

Figure 3. Estimated cumulative incidence of locoregional recurrence and death before locoregional recurrence in melanoma patients followed with and without routine FDG PET-CT scans: Data from 1,480 Danish stage IIB-IIID patients.

Legend: Cumulative incidence of locoregional recurrence and death before locoregional recurrence in 715 stage IIB-IIID melanoma patients followed with clinical examinations and routine FDG PET-CT (primary diagnosis in 2016-2017) compared to 765 patients followed with clinical examinations alone (primary diagnosis in 2008-2010). Abbreviations: Competing event = death before locoregional recurrence, mo = months, yr = year, yrs = years.

Figure 4. Estimated cumulative incidence of distant recurrence and death before distant recurrence in melanoma patients followed with and without routine FDG PET-CT scans: Data from 1,480 Danish stage IIB-IIID patients.

Legend: Cumulative incidence of distant recurrence and death before distant recurrence in 715 stage IIB-IIID melanoma patients followed with clinical examinations and routine FDG PET-CT (primary diagnosis in 2016-2017) compared to 765 patients followed with clinical examinations alone (primary diagnosis in 2008-2010). Abbreviations: Competing event = death before distant recurrence, mo = months, yr = year, yrs = years.

Tables

Table 1. Demographic and clinical characteristics of 1,480 Danish patients with AJCC8 pathological stage IIB-IIID melanoma.

	2008-2010	2016-2017	p
n (%)	765 (51.7)	715 (48.3)	
Follow-up time, *median [IQR]*[1]	10.8 [3.4 – 12.4]	4.5 [2.8 – 5.2]	
Age, *median [IQR]*	63 [50 - 75]	69 [54 - 78]	<0.001
Age group, *n (%)*			
<40 years	91 (11.9)	51 (7.1)	
40-64 years	319 (41.7)	244 (34.1)	<0.001
>=65 years	355 (46.4)	420 (58.7)	
Sex, *n (%)*			
Female	369 (48.2)	300 (42.0)	<0.018
Male	396 (51.8)	415 (58.0)	
Charlson comorbidity index, *n (%)*			
Low	336 (43.9)	226 (31.6)	
Medium	271 (35.4)	257 (35.9)	<0.001
High	158 (20.7)	232 (32.4)	
AJCC8 Pathological stage			
IIB	179 (23.4)	158 (22.1)	
IIC	84 (11.0)	100 (14.0)	
IIIA	134 (17.5)	113 (15.8)	0.528
IIIB	177 (23.1)	156 (21.8)	
IIIC	176 (23.0)	173 (24.2)	
IIID	15 (2.0)	15 (2.1)	
Histopathological subtype, *n (%)*			
Superficial spreading melanoma	396 (51.8)	380 (53.1)	
Nodular melanoma	198 (25.9)	125 (17.5)	
Lentigo maligna melanoma	< 15 (< 2.0)	11 (1.5)	<0.001
Acrolentiginous melanoma	19 (2.5)	14 (2.0)	
Desmoplastic melanoma	< 5 (< 0.7)	6 (0.8)	
Unclassifiable	51 (6.7)	51 (7.1)	

Unknown	88 (11.5)	128 (17.9)	
Localization, *n (%)*			
Head and neck	97 (12.7)	103 (14.4)	
Trunk	345 (45.1)	298 (41.7)	
Upper extremities	96 (12.5)	107 (15.0)	
Lower extremities	206 (26.9)	179 (25.0)	0.016
Genitalia	< 10 (< 1.3)	< 15 (< 2.1)	
Unknown primary tumor	< 5 (< 0.7)	< 15 (< 2.1)	
Unknown	11 (1.4)	< 5 (< 0.7)	
Events, $n_{patients}$ *(%)*			
Recurrence[2]			
Overall recurrence	302 (39.5)	261 (36.5)	
Locoregional recurrence	180 (23.5)	137 (19.2)	
Distant recurrence	224 (29.3)	212 (29.7)	
Death by cause			
Death from melanoma	220 (53.8)	151 (55.3)	
Death from other causes	189 (46.2)	122 (44.7)	
Censoring	14 (1.8)	5 (0.7)	
Emigration	< 5 (< 0.7)	< 5 (< 0.7)	
New melanoma of higher stage	< 15 (< 2.0)	< 5 (< 0.7)	

Legend: Table 1. Demographic and clinical characteristics of 1,480 Danish patients with AJCC8 pathological stage IIB-IIID melanoma. 1) All time variables are reported in years. 2) Recurrence reported as number of patients with at least one recurrence during study period, n (%). Abbreviations: IQR = Interquartile range.

Table 2. Estimated cumulative incidence of recurrence in 1,480 stage IIB-IIID melanoma patients followed with and without routine FDG PET-CT.

Year of diagnosis	Time	Overall recurrence	Death before event	Locoregional recurrence	Death before event	Distant recurrence	Death before event
2008-2010	6 months	6.5 (4.8 - 8.3)	1.4 (0.6 - 2.3)	3.3 (2.0 - 4.5)	1.7 (7.8 - 2.6)	3.5 (2.2 - 4.8)	1.6 (0.7 - 2.5)
n = 765	1 year	13.1 (10.7 - 15.5)	4.2 (2.8 - 5.6)	8.0 (6.1 - 9.9)	5.2 (3.7 - 6.8)	7.2 (5.4 - 9.0)	4.8 (3.3 - 6.4)
	2 years	22.1 (19.2 - 25.1)	7.2 (5.4 - 9.0)	13.5 (11.1 - 15.9)	10.7 (8.5 - 12.9)	13.2 (10.8 - 15.6)	8.5 (6.5 - 10.5)
	3 years	27.5 (24.3 - 30.7)	8.9 (6.9 - 10.9)	16.6 (14.0 - 19.3)	14.8 (12.3 - 17.3)	18.5 (15.7 - 21.2)	11.0 (8.8 - 13.2)
	5 years	34.2 (30.8 - 37.5)	12.3 (10.0 - 14.6)	20.4 (17.6 - 23.3)	21.9 (18.9 - 24.8)	23.8 (20.8 - 26.8)	15.7 (13.1 - 18.3)
2016-2017	6 months	6.3 (4.5 - 8.1)	2.1 (1.0 - 3.1)	4.1 (2.6 - 5.5)	2.2 (1.2 - 3.3)	3.5 (2.2 - 4.8)	2.5 (1.4 - 3.7)
n = 715	1 year	17.5 (14.7 - 20.3)	4.2 (2.7 - 5.7)	10.9 (8.6 - 13.2)	5.9 (4.2 - 7.6)	12.6 (10.2 - 15.0)	5.3 (3.7 - 7.0)
	2 years	26.9 (23.6 - 30.1)	8.5 (6.5 - 10.6)	15.4 (12.8 - 18.0)	12.9 (10.4 - 15.3)	21.0 (18.0 - 24.0)	10.8 (8.5 - 13.1)
	3 years	32.3 (28.9 - 35.8)	11.8 (9.4 - 14.1)	17.9 (15.1 - 20.7)	18.6 (15.8 - 21.5)	25.8 (22.6 - 29.0)	14.6 (12.0 - 17.2)
	5 years	36.9 (33.3 - 40.5)	16.7 (13.9 - 19.5)	19.3 (16.4 - 22.2)	28.0 (24.6 - 31.4)	29.8 (26.4 - 33.2)	20.5 (17.5 - 23.6)

Legend: All cumulative incidence rates reported as % (95% CI). Time is measured from finalized primary treatment

Table 3. Hazard ratio and absolute risk of overall, locoregional, and distant recurrence in 715 stage IIB-IIID melanoma patients followed with clinical examinations and routine FDG PET-CT compared to 765 patients followed with clinical examinations alone.

	Hazard ratio		Absolute risk of event or competing event within 2 years			
			Event		Death before event	
	Event	Death before event	2008-2010	2016-2017	2008-2010	2016-2017
Overall recurrence						
Study period	**1.01 (0.85 - 1.21)**	**1.25 (0.94 - 1.63)**				
within two years	**1.16 (0.93 - 1.44)**	**1.01 (0.69 - 1.47)**	**13.8 (8.1 – 21.1)**	**18.1 (12.9 – 24.2)**	**3.3 (1.3 – 4.8)**	**2.7 (1.4 – 6.7)**
IIB	1.71 (1.02 - 2.89)	1.34 (0.70 - 2.56)	9.0 (4.6 – 15.1)	12.0 (7.2 – 18.2)	4.2 (1.6 – 8.7)	3.5 (1.5 – 6.7)
IIC	1.12 (0.59 - 2.10)	1.23 (0.62 - 2.43)	13.1 (6.0 – 23.0)	17.4 (9.4 – 27.4)	6.1 (2.3 – 12.7)	5.0 (2.1 – 9.9)
IIIA	0.67 (0.33 - 1.39)	NA	6.8 (3.3- 12.1)	9.1 (5.1 – 14.6)	1.2 (0.3 – 3.6)	1.0 (0.3 – 2.8)
IIIB	1.16 (0.70 - 1.92)	0.52 (0.15 - 1.86)	9.5 (5.1 – 15.5)	12.7 (8.2 – 18.3)	2.5 (1.0 – 5.4)	2.1 (0.9 – 4.1)
IIIC	1.07 (0.76 - 1.49)	0.66 (0.30 - 1.46)	24.7 (13.8 – 37.2)	32.1 (22.1 – 42.4)	5.7 (2.2 - 11.7)	4.6 (2.0 – 8.7)
IIID	1.67 (0.69 - 4.04)	2.53 (0.20 - 31.21)	58.8 (31.4 – 78.4)	70.2 (45.3 – 45.3)	10.8 (3.2 – 24.0)	7.9 (2.6 – 17.4)
after two years	**0.81 (0.60 - 1.11)**	**1.42 (0.95 - 2.12)**				
IIB	1.03 (0.53 - 2.01)	1.03 (0.53 - 2.01)				
IIC	0.66 (0.25 - 1.72)	0.66 (0.25 - 1.71)				
IIIA	0.40 (0.16 - 1.01)	0.40 (0.16 - 1.01)				
IIIB	1.05 (0.58 - 1.90)	1.05 (0.58 - 1.90)				
IIIC	0.81 (0.46 - 1.44)	0.81 (0.46 - 1.44)				
IIID	NA	NA				
Locoregional recurrence						
Study period	**0.84 (0.66 - 1.06)**	**1.11 (0.90 - 1.38)**				
within two years	**1.05 (0.79 - 1.39)**	**0.99 (0.73 - 1.35)**	**12.9 (6.9 – 20.9)**	**14.5 (9.7 – 20.2)**	**2.6 (1.1 – 5.3)**	**2.2 (1.0 – 4.1)**
IIB	1.51 (0.74 - 3.09)	1.40 (0.79 - 2.46)	8.1 (3.7 – 14.7)	9.1 (5.0 – 14.8)	3.2 (1.2 – 6.9)	2.8 (1.2 – 5.6)
IIC	0.82 (0.37 - 1.84)	1.24 (0.67 - 2.28)	13.2 (5.2 – 24.9)	14.8 (7.1 – 25.1)	4.8 (1.7 – 10.4)	4.2 (1.7 – 8.5)
IIIA	0.86 (0.34 - 2.18)	0.43 (0.04 - 4.81)	6.1 (2.6 – 12.0)	6.9 (3.4 – 12.1)	1.0 (0.2 – 3.1)	0.9 (0.2 – 2.5)
IIIB	1.09 (0.55 - 2.14)	0.52 (0.20 - 1.36)	8.3 (3.9 – 14.8)	9.3 (5.4 – 14.6)	1.9 (0.7 – 4.2)	1.6 (7.0 – 3.3)
IIIC	1.00 (0.65 - 1.51)	0.84 (0.47 - 1.49)	24.8 (12.7 – 38.9)	27.6 (17.8 – 38.3)	4.3 (1.6 – 9.1)	3.7 (1.6 – 7.3)

IIID	1.19 (0.40 - 3.49)	0.49 (0.11 - 2.21)	52.4 (22.7 – 75.5)	57.0 (30.1 – 76.9)	7.4 (2.2 – 17.1)	6.2 (2.0 – 14.0)
after two years	**0.53 (0.33 - 0.84)**	**0.81 (0.60 - 1.11)**				
IIB	0.32 (0.09 - 1.11)	1.03 (0.53 - 2.01)				
IIC	0.28 (0.06 - 1.35)	0.66 (0.25 - 1.72)				
IIIA	0.17 (0.02 - 1.32)	0.40 (0.16 - 1.01)				
IIIB	0.70 (0.32 - 1.55)	1.05 (0.58 - 1.90)				
IIIC	0.82 (0.37 - 1.83)	0.81 (0.46 - 1.44)				
IIID	NA	NA				
Distant recurrence						
Study period	**1.20 (0.98 - 1.46)**	**1.20 (0.94 - 1.53)**				
Within two years	**1.51 (1.16 - 1.96)**	**1.07 (0.76 - 1.51)**	**10.4 (5.7 – 16.7)**	**15.0 (10.2 – 20.7)**	**1.4 (0.5 – 3.0)**	**1.4 (0.6 – 2.8)**
IIB	2.61 (1.32 - 5.16)	1.38 (0.74 - 2.56)	6.6 (3.2 – 11.8)	9.9 (5.6 – 15.5)	1.8 (0.6 – 4.2)	1.8 (0.7 – 4.0)
IIC	1.29 (0.62 - 2.67)	1.35 (0.69 - 2.65)	10.6 (4.4 – 19.8)	15.6 (7.8 – 25.7)	2.8 (0.9 – 6.7)	2.9 (1.0 – 6.4)
IIIA	1.40 (0.52 - 3.77)	1.02 (0.06 - 16.46)	4.2 (1.8 – 8.1)	6.2 (3.2 – 10.7)	0.3 (0.1 – 1.3)	0.3 (0.1 – 1.3)
IIIB	1.67 (0.89 -3.12)	0.49 (0.17 - 1.40)	7.1 (3.4 – 12.1)	10.5 (6.5 – 15.6)	1.0 (0.3 – 2.4)	1.0 (0.4 – 2.3)
IIIC	1.27 (0.85 -1.90)	0.85 (0.44 - 1.64)	18.7 (9.9 – 29.5)	26.8 (17.8 – 36.6)	2.5 (0.8 – 5.7)	2.5 (0.9 – 5.3)
IIID	1.29 (0.49 - 3.42)	1.35 (0.28 - 6.47)	53.9 (25.7 – 75.5)	68.6 (40.4 – 85.5)	5.4 (1.5 – 13.3)	4.7(1.4 – 11.3)
After two years	**0.86 (0.62 - 1.20)**	**1.28 (0.90 - 1.82)**				
IIB	1.58 (0.79 - 3.18)	1.53 (0.84 - 2.76)				
IIC	0.72 (0.28 - 1.87)	1.27 (0.62 - 2.61)				
IIIA	0.38 (0.14 - 1.04)	2.11 (0.47 - 9.46)				
IIIB	1.44 (0.74 - 2.80)	0.93 (0.40 - 2.18)				
IIIC	0.57 (0.31 - 1.06)	1.23 (0.55 - 2.78)				
IIID	NA	NA				

Legend: Table T3. Hazard ratio and absolute risk of overall, locoregional, and distant recurrence in 715 stage IIB-IIID melanoma patients followed with clinical examinations and routine FDG PET-CT compared to 765 patients followed with clinical examinations alone. Hazard ratios (HR) reported for full study period and for subperiods within and after two years from finalized primary treatment. Subperiod HR is further reported for each stage. Cause-specific hazards-models were adjusted for sex, age, Charlson comorbidity-index and histological subtype. Death before event included death from all causes. Absolute risk was calculated for a patient of fixed risk factor values (male sex, medium comorbidity-index, superficial spreading subtype, age 40-64 years). Abbreviations: HR = Hazard ratio.