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Review – Prostate Cancer

## Exploring All Avenues for Radiotherapy in Oligorecurrent Prostate Cancer Disease Limited to Lymph Nodes: A Systematic Review of the Role of Stereotactic Body Radiotherapy

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### Abstract

**Context:** Stereotactic body radiotherapy (SBRT) is emerging as a treatment option in patients affected by oligorecurrent prostate cancer disease limited to lymph nodes, a subgroup of patients who would otherwise be treated only with androgen deprivation therapy (ADT).

**Objective:** To perform a systematic review of SBRT for oligorecurrent prostate cancer limited to lymph nodes.

**Evidence acquisition:** We performed a systematic review of PubMed/Medline in October 2016 according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). We searched for studies reporting on biochemical or clinical progression and/or toxicity or complications of SBRT. Reports were excluded if these end points could not be ascertained or separately analyzed, or if insufficient details were provided.

**Evidence of synthesis:** A total of 363 patients from nine studies were collected. Of these patients, 211 were treated with SBRT for a total of 270 lymph nodes. With an alpha–beta ratio of 3 Gy, the biologically effective dose in fractionated SBRT was >100 Gy in all studies (range, 88–216 Gy). With a median follow-up of 19.23 mo, local control was achieved in 98.1% of patients. Median progression-free survival (defined as biochemical and/or radiological progression) was 22.5 mo (range, 11–30 mo). Information about ADT during SBRT was available in 281 patients, of whom 114 (40.5%) were on ADT during SBRT, and the duration of hormone therapy ranged from 1 to 17.5 mo. Median ADT-free survival was 32.8 mo (range, 25–44 mo). About toxicity, Common Terminology Criteria for Adverse Events toxicity scale was most used. Acute and/or late grade  $\geq 2$  toxicity was reported in only 5.6% of patients, and no patient developed grade 4 toxicity.

**Conclusions:** SBRT seems to be promising in lymph node oligorecurrent prostate cancer, although there is a weak level of evidence to support such investigational treatment, which is currently based on retrospective studies of single-institution or pooled experiences. ADT-free survival is an interesting end point, which needs to be investigated.

**Patient summary:** We performed a systematic review to assess outcomes and toxicity of stereotactic body radiotherapy (SBRT) for patients affected by oligorecurrent prostate cancer limited to lymph nodes. We concluded that SBRT is a promising therapy in this setting, but it needs to be validated in randomized controlled trials.

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## 1. Introduction

Stereotactic body radiotherapy (SBRT) is emerging as an appropriate treatment option in patients affected by limited metastatic disease, defined as “oligometastatic state,” which is considered as an intermediate state between localized and widespread cancer, and seems to be characterized by a unique biological profile [1]. In such patients with a limited number of metastases (<3 or <5) from a variety of primary sites, it seems that local therapy (surgery or ablative radiotherapy) might improve overall survival and disease progression-free survival (PFS), and delay the need for systemic therapy [2–6]. In this therapeutic scenario, SBRT seems to be a safe treatment option with a very low toxicity profile, and without the morbidity and risk associated with surgical procedures [7].

In oligorecurrent prostate cancer patients, who eventually develop a low burden of disease after curative treatment, SBRT could mean an appropriate therapeutic strategy with curative intent. SBRT could also defer palliative androgen deprivation therapy (ADT), which is currently the standard of care for such patients, despite the fact that it can have a detrimental effect on their quality of life. The subset of prostate cancer patients with oligorecurrence confined to lymph nodes represents a very early metastatic setting in which local treatment such as SBRT might have a great impact on disease control [8–10].

The aim of our study was to review the available literature on SBRT for lymph node recurrent prostate cancer patients, in order to evaluate efficacy and toxicity of this high-precision noninvasive ablative treatment in such an early metastatic setting. In the Discussion section, we also provide an analysis of the major studies investigating the role of prophylactic irradiation of regional lymph nodes in the same setting of patients.

## 2. Evidence acquisition

We searched for articles reporting on oncological outcome (biochemical response and/or PFS) and toxicity of prostate cancer patients, affected by oligorecurrent disease limited to lymph nodes and treated with SBRT. SBRT was defined as a radiotherapy dose of at least 5 Gy per fraction to a biologically effective dose of 80 Gy with an alpha–beta ratio of 3 Gy. A PubMed literature search was conducted using the Preferred Reporting Items and Meta-Analyses (PRISMA) [11]. We identified articles published within the last 10 yr up to September 30, 2016, using Medline search with the following selection criteria: English language, full papers, oligorecurrent prostate cancer limited to lymph nodes treated with SBRT, and oncological and toxicity data available. The following Medline terms were used: prostate cancer, lymph node metastasis, lymph node recurrence, oligometastatic prostate cancer, oligorecurrent prostate cancer, stereotactic radiotherapy, stereotactic body radiotherapy, radiosurgery, and stereotactic ablative radiotherapy. If multiple publications from the same center were available, the most recent one was selected. We reviewed the full version of each article. The following information was abstracted

from all primary reports: primary author, reference, year of publication, number of patients, patient population, age, number of patients treated with SBRT for node metastasis, number of irradiated metastases, study design, treatment of the primary prostate cancer, dose and fractionation of SBRT, oncological outcome (PFS and overall survival), local control, prognostic factors (univariate and multivariate), and toxicity.

## 3. Evidence synthesis

The flowchart of the systematic review is reported in Fig. 1. In total, 363 patients from nine studies [12–20] were collected (Table 1). Of these patients, 211 were treated with SBRT for a total of 270 lymph nodes (Table 2). In Table 3, we reported the site (pelvic or extrapelvic) of nodes irradiated with SBRT: 162 (76.7%) patients were affected by pelvic oligorecurrence. Information about the primary treatment was available in 334 (92%) patients: 250 (75%) underwent radical prostatectomy ± radiotherapy ± ADT, 78 (23.3%) underwent radiotherapy ± ADT, and six (1.7%) received chemotherapy as primary treatment.

Median time from primary treatment to oligorecurrent disease was available only in seven studies (Table 1), with an overall median value of 37.45 mo (range, 11.5–75.6 mo). Choline-positron emission tomography (PET)/computed tomography (CT) was used in almost all studies to detect disease in patients with biochemical recurrence after primary treatment. The median prostate-specific antigen (PSA) value at oligorecurrent disease, available in six studies, was 4.2 ng/ml (range, 1.77–16 ng/ml). Median follow up was 21.9 mo (range, 4.4–36 mo).

SBRT was delivered with a linear accelerator in almost all studies (Table 2). Several radiotherapy schedules were used, varying from 5 to 11 Gy per fraction, to a total dose of 25–50 Gy, whereas four metastatic nodes were irradiated using a single fraction (range, 12–24 Gy). With an alpha–beta ratio of 3 Gy, the biologically effective dose in fractionated SBRT was >100 Gy in all studies (range, 88–216 Gy). The median gross tumor volume–planning target volume margin was 5 mm. In all studies, image guidance was used prior to radiotherapy delivery.

Between studies, biochemical recurrence after SBRT was defined in different ways: some authors considered it as a

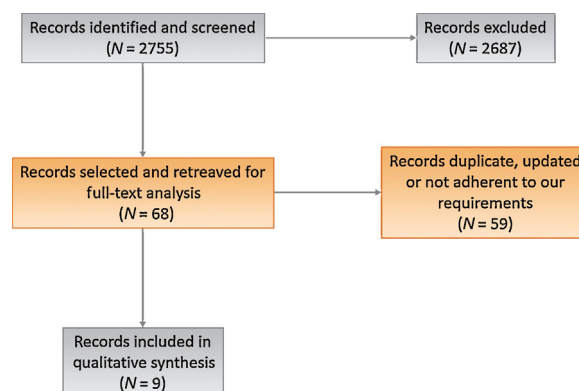


Fig. 1 – Flowchart of the systematic review.

**Table 1 – Patient characteristics.**

Study	No. of pts (total)	Age (median)	No. of pts treated for nodes	Median time to metastatic recurrence (mo)	Median PSA at time of node metastasis (ng/ml)	Staging method	Median FU (mo)	ADT	No. of pts in ADT	Median duration of ADT (mo)
Casamassima et al (2011) [12]	25	66 <sup>a</sup>	25	11.8–36.7	5.65	Choline-PET (100%)	29	No	–	–
Jerezek-Fossa et al (2012) [13]	34	68.3	18	66 (mean)	1.77; 10.7 <sup>b</sup>	Choline-PET (100%)	21.9; 13.7 <sup>b</sup>	Yes	14 (78%)	17.5; 12 <sup>b</sup>
Ahmed et al (2013) [14]	17	65	1	50.4	NR	Choline-PET (53%), MRI (47%)	4.4	Yes	1 (100%)	NR
Decaestecker et al (2014) [15]	50	59 <sup>a</sup>	27	57.6	5.1	Choline-PET (36%), FDG-PET (64%)	24	Yes	35 (70%)	1
Deti et al (2015) [16]	30	64 <sup>a</sup>	30	75.6	16	Choline-PET (100%)	12	Yes	14 (46%)	NR
Muldermans et al (2016) [17]	66	61.4 <sup>a</sup>	5	NR	NR	Choline-PET (70%), MRI (12%), CT (3%)	16	NR	NR	NR
Pasqualetti et al (2016) [18]	29	71.2	17	11.5	3.43 (mean)	Choline-PET (100%)	11.5	No	–	–
Ingrosso et al (2016) [19]	40	74	40	37.4	4.2	Choline-PET (100%)	23.8	Yes	19 (47%)	NR
Ost et al (2016) [20]	72	60 <sup>a</sup>	72	44.4	3.4	Choline-PET (75%), FDG-PET (24%), MRI (1%)	36	Yes	31 (43%)	1

ADT = androgen deprivation therapy; FDG = fludeoxyglucose; FU = follow-up; MRI = magnetic resonance imaging; NR = not reported; PET = positron emission tomography; PSA = prostate-specific antigen; pts = patients.

<sup>a</sup> Mean value.

<sup>b</sup> Two patients with retroperitoneal node metastasis.

**Table 2 – Treatment characteristics.**

Study	No. of nodes (total)	No. of pts treated with SBRT for node metastases	No. of nodes treated with SBRT	Median GTV (cc)	Median GTV–PTV margin (mm)	Linac/Cyber knife	SBRT schedule	Dose prescription	BED ( $\alpha/\beta = 3$ )
Casamassima et al (2011) [12]	25	18	18	NR	5	Linac	3 × 10 Gy	To the isodose covering 95% of the PTV	130
Jerezek-Fossa et al (2012) [13]	18	18	18	NR	2	Cyber	3 × 11 Gy; 3 × 12 Gy (in 2 pts M1)	To the mean 80% isodose	154–165
Ahmed et al (2013) [14]	1	1	1	NR	5	Linac	5 × 10 Gy	NR	130
Decaestecker et al (2014) [15]	27	27	27	NR	3	Linac	3 × 10 Gy; 5 × 10 Gy	80% of the prescribed dose covering 90% of the PTV	130–133
Deti et al (2015) [16]	39	30	39	NR	2	Cyber	1 × 24 Gy; 5 × 6 Gy; 3 × 9 Gy; 3 × 10 Gy; 3 × 12 Gy	NR	180–216
Muldermans et al (2016) [17]	6	5	6	NR	5	Linac	1 × 24 Gy; 1 × 16 Gy; 5 × 10 Gy; 3 × 10 Gy	AAPM 101	101–133
Pasqualetti et al (2016) [18]	25	NR	25	2.9 (mean)	3	Linac	1 × 24 Gy; 3 × 9 Gy	To the periphery of the target	64.8–129.6
Ingrosso et al (2016) [19]	47	40	47	3	5–8	Linac	1 × 12 Gy; 5 × 10 Gy; 5 × 8 Gy; 4 × 8 Gy; 5 × 7 Gy; 5 × 6 Gy; 5 × 5 Gy	95% of the dose to the 95% of the PTV	36–130
Ost et al (2016) [20]	89	72	89	NR	2–7	Linac/Cyber	3 × 10 Gy; 3 × 8 Gy; 5 × 6 Gy; 10 × 5 Gy	NR	88–140

BED = biologically effective dose; GTV = gross tumor volume; NR = not reported; pts = patients; PTV = planning target volume; SBRT = stereotactic body radiotherapy.

**Table 3 – Site (pelvic or extrapelvic) of nodes treated with SBRT.**

	Total no. of patients treated with SBRT	Total no. of nodes treated with SBRT	Pelvic (no. of pts/no. of nodes)	Extrapelvic (no. of pts/no. of nodes)
Casamassima et al (2011) [12]	18	18	15 (pelvic and/or extrapelvic)/NR	3 (mediastinal)/NR
Jereczek-Fossa et al (2012) [13]	18	18	16/16	2/2
Ahmed et al (2013) [14]	1	1	0	1/1
Decaestecker et al (2014) [15]	27	27	25/25	2/2
Detti et al (2015) [16]	30	39	NR/27	NR/12
Muldermans et al (2016) [17]	5	6	NR	NR
Pasqualetti et al (2016) [18]	NR	25	NR/18	NR/7
Ingrosso et al (2016) [19]	40	47	35/40	5/7
Ost et al (2016) [20]	72	89	53/NR	19/NR

NR = not reported; pts = patients; SBRT = stereotactic body radiotherapy.

single PSA increase without a cutoff value, while others defined it as two consecutive increases of  $\geq 20$ –25% compared with the pre-SBRT value, or simply two consecutive increases. Radiological PFS was defined as the presence of new metastases after SBRT, or the presence of in-field recurrence and/or new metastases. Follow-up evaluation consisted in PSA every 2–3 mo and choline-PET 3–6 mo after SBRT.

Local control was achieved in 98.1% of patients, and PFS (defined as biochemical and/or radiological progression) ranged between 11 and 30 mo with a median value of 22.5 mo (Table 4). Only in two studies, there was an in-field recurrence (for a total of four patients).

Data on concomitant ADT (Table 1) were available in eight studies (in two of them no ADT was combined with SBRT), for a total of 281 patients. Of the 114 (40.5%) patients who were on ADT during SBRT, the duration of hormone therapy ranged from 1 to 17.5 mo (Table 1). ADT-free survival, ranging from 25 to 44 mo with a median value

of 32.8 mo (Table 4), was available only in four studies (including 191 patients), and this means that in 106/191 (55.5%) patients there could be a potential important delay in the start of ADT.

About toxicity, the Common Terminology Criteria for Adverse Events toxicity scale was the most used, whereas Radiation Therapy Oncology Group scale was used in three studies (Table 4). Acute and/or late grade  $\geq 2$  toxicity was reported in only 5.6% of patients, and no patient developed grade 4 toxicity. More specifically, two patients experienced acute toxicity  $\geq 2$  [13,19] and late toxicity was reported in five patients (three patients with grade 2 and two patients with grade 3) [13,15,19,20].

### 3.1. Discussion

Oligorecurrent prostate cancer limited to lymph nodes may be a very favorable clinical condition. The present work underlines the role of ablative SBRT in the management of

**Table 4 – Results.**

Study	Median PFS (mo)	b-RFS (mo)	Toxicity scale	FU evaluation	In-field recurrence	ADT-FS (mo)	RECIST criteria	No. of pts with acute and/or late toxicity (grade $\geq 2$ )
Casamassima et al (2011) [12]	24	NR	RTOG	PSA every 3 mo, choline-PET at 2 mo	No	NR	NR	0
Jereczek-Fossa et al (2012) [13]	>30; 11 <sup>a</sup>	NR	RTOG	PSA every 3 mo and choline-PET (timing not reported)	No	NR	Yes	1 (acute); 2 (late)
Ahmed et al (2013) [14]	NR	NR	CTCAE 3.0	PSA every 3 mo and imaging at 3 mo	No	NR	Yes	0
Decaestecker et al (2014) [15]	19	NR	CTCAE 3.0	PSA every 3 mo and choline-PET at PSA progression	No	25	Yes	3 (late)
Detti et al (2015) [16]	NR	8.1	CTCAE 4.0	PSA every 3 mo and imaging at PSA progression	No	NR	Yes	1 (acute)
Muldermans et al (2016) [17]	NR	NR	CTCAE 4.0	PSA every 3 mo and choline-PET at 3–6 mo	No	NR	Yes	0
Pasqualetti et al (2016) [18]	NR	NR	CTCAE 4.0	PSA every 3 mo and choline-PET at 3–6 mo	No	39.7	Yes	0
Ingrosso et al (2016) [19]	15.5	24	RTOG	PSA every 3 mo and choline-PET at PSA progression	Yes (1 pt)	26 (mean)	Yes	1 (acute); 1 (late)
Ost et al (2016) [20]	21	NR	CTCAE 4.0	PSA every 3 mo and choline-PET at 3–6 mo	Yes (3 pts)	44	Yes	3 (late)

ADT-FS = androgen deprivation therapy-free survival; b-RFS = biochemical relapse-free survival; FU = follow-up; NR = not reported; PET = positron emission tomography; PFS = progression-free survival; PSA = prostate-specific antigen; pts = patients; RECIST = response evaluation criteria in solid tumors; RTOG = Radiation Therapy Oncology Group.

<sup>a</sup> Two patients with retroperitoneal node metastasis.

patients affected by lymph node oligorecurrent disease, a subgroup of patients who would otherwise be treated only with delayed or immediate ADT [21], which affects patients' quality of life in multiple spheres.

Choline-PET was the most used staging modality at diagnosis of oligorecurrence. In fact, it was employed in 100% of cases in five studies and from 36% to 75% in the remaining four (Table 1); however, this imaging technique, with either 18F-fluoromethylcholine or 11C-choline, has a low detection rate [22,23] at low PSA levels, a setting in which a targeted salvage therapy might result in better outcome. Currently, many patients being treated with ablative therapy for oligometastatic disease actually have undetectable micrometastases that will cause mainly oligoprogression rather than widespread disease [20]. In a recent retrospective analysis, Ost et al [20] found that after SBRT for nodal prostate cancer oligometastases, the pattern of relapse was mainly nodal and oligometastatic. This modality of progression might give the possibility of a repeated SBRT strategy, similarly to what has been described for brain metastasis stereotactic radiotherapy [24]. In these patients, also the combination of prophylactic regional nodal irradiation and ablative boost to the nodal lesion could be a treatment option. For instance, Rischke et al [25] reported that prophylactic nodal irradiation added to salvage lymph node dissection results in a significant delay of node relapse within the treated region compared with surgery only (5-yr relapse-free rate 70.7% vs 26.3%,  $p < 0.0001$ ). Other studies on prophylactic irradiation on lymph node chains adjacent to PET-positive nodes reported a good outcome with grade  $\geq$  toxicity rates ranging from 15% to 25% [26,27].

In the recent past, regional lymph node dissection in oligorecurrent prostate cancer limited to lymph nodes has been proposed to reduce disease burden, improve the efficacy of ADT, and delay clinical progression [28,29]. In the same way, regional lymph node irradiation, such as whole-pelvis radiotherapy (wpRT), has been evaluated [26,30,31]. The series by Schick et al [30] analyzed 43 patients affected by  $\leq 4$  metachronous prostate cancer metastatic nodes. More specifically, 21 patients received radiotherapy for pelvic lymph node metastases and five for both pelvic and extrapelvic node metastases. This subset of 26 patients received wpRT (total median dose 50.4 Gy) with a boost (total median dose 65 Gy) to the choline-PET-positive nodes, in addition to limited ADT (median 12 mo). At 3 yr, biochemical relapse-free survival (b-RFS) was 54.5%, clinical failure-free survival (defined as the time from radiotherapy to the development of new metastases) 58.6%, and overall survival 91.7%. Fodor et al [26] published the results of a phase II trial on choline-PET-guided radiotherapy analyzing 3 yr toxicity and outcome in 83 patients affected by lymph node relapse after primary treatment. Fifty-eight (71.6%) patients received concomitant/adjuvant ADT for a median time of 12 mo. Regarding radiotherapy, the areas of microscopic involvement included in the clinical target volume were the regional lymph node chains or only the lymphatic chain including choline-PET-positive nodes, depending on overlap with previously irradiated volumes for primary treatment. Seventy-two patients were

irradiated at the pelvic and/or lumbar-aortic lymph nodes. The total dose for prophylactic irradiation was 51.8 Gy in 28 fractions. The total dose in the simultaneous integrated boost of the choline-PET-positive nodes was 65.5 Gy. Three-year actuarial overall, local relapse-free survival, and clinical relapse-free survival (defined as new metastases) were 80%, 89.8%, and 61.8%, respectively. The 3-yr b-RFS was 42.2%. The presence of extrapelvic lymph node disease and the number of PET-positive nodes negatively influenced clinical relapse. Regarding toxicity, the 3-yr actuarial grade  $\geq 2$  rectal and genitourinary toxicities were 6.6% and 26.3%, respectively. Würschmidt et al [27] reported a 3-yr b-RFS of 49% and a median survival of 28.3 mo in 19 patients who received wpRT (total dose 45 Gy in 3D conformal irradiation, 50.4 Gy in intensity-modulated radiation therapy) with a boost (median total dose 66.6 Gy) to the choline-PET-positive nodes. At 28 mo, 75% of patients were free from new metastases. In the total cohort, acute and late grade  $\geq 2$  toxicities were 15% and 16%, respectively.

New imaging tools such as 68Ga-PSMA-11 PET could improve the treatment selection by detecting oligorecurrent disease in an early stage or by upstaging an apparent oligorecurrent disease. When compared with 11C-choline PET, 68Ga-PSMA-11 PET demonstrated a significantly higher detection rate of lymph node metastasis (71% vs 94%,  $p < 0.001$ ) [32]. In particular, its higher detection rate for local relapse, lymph nodes, and bone lesions with respect to 18F-fluoromethylcholine or 11C-choline PET is more evident at a low PSA value ( $< 1$  ng/ml) [32–34]. Finally, the comparison with histology data revealed high diagnostic accuracy of PSMA-PET (per lesion specificity of 97% and sensitivity of 80%; per patient specificity and sensitivity both of 86%) [35]. Other imaging options are whole-body magnetic resonance, which is useful for the detection of bone metastases [36,37] but less suited for lymph node recurrence [38], and magnetic resonance lymphography with iron oxide nanoparticles, which has high sensitivity (65–92%) and specificity (93–98%) [39] but is currently not commercially available.

Advances in diagnostic imaging as well as novel biomarkers will lead to a better selection of patients with a low burden of disease, who could be treated only with localized ablative radiotherapy, obviating the need of regional prophylactic nodal irradiation and postponing systemic therapy.

Although SBRT seems to be promising in lymph node oligorecurrent prostate cancer, which is usually a slowly growing tumor, there is a weak level of evidence to support such treatment. In fact, the main limitation of the reported studies in our review is their retrospective nature, based on single-institution or pooled experiences. The other limitation is the small number of patients included in each series. No data on tumor volume were reported in almost all studies.

Ongoing randomized phase 2 clinical trials, such as the STOMP [40] and ORIOLE [41], will assess the impact of ablative radiotherapy in terms of overall survival, PFS, ADT-free survival, and quality of life in patients with  $\leq 3$  metastases, compared with the standard of care. Another



phase 2 trial [42] will address the role of wpRT in patients affected by  $\leq 5$  pelvic oligometastases versus ADT.

#### 4. Conclusions

The standard treatment option in lymph node oligorecurrent prostate cancer patients is palliative ADT until resistance, but metastasis-directed therapy seems to be promising in this setting, although the optimal salvage treatment needs to be identified by prospective trials. A lower PSA doubling time and a smaller number of metastases could help identify the best candidates for SBRT.

According to retrospectively collected data, SBRT is safe (with toxicity rates ranging from 0% to 15%), achieves high local control rate (near to 100%), and has a positive impact on PFS. An interesting end point is ADT-free survival, based on patient-reported compliance to such a truly impactful treatment. Hence, further investigation on this end point is needed.

In the near future, clinical, biological, and genomic features will better define oligorecurrent disease, and this will lead to the stratification of different prognostic classes. It is likely that in selected patients SBRT alone will be the treatment of choice, whereas in other cases there would be a need for treatment intensification.

**Author contributions:** Gianluca Ingrosso had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Ponti, Lancia, Ingrosso.

**Acquisition of data:** Ponti, Lancia, Ingrosso, Detti.

**Analysis and interpretation of data:** Ponti, Lancia, Ingrosso, Ost.

**Drafting of the manuscript:** Ponti, Lancia, Ingrosso, Trippa, Triggiani.

**Critical revision of the manuscript for important intellectual content:** Ost, Detti.

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