Gynecologic Oncology 155 (2019) 229–236

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Primary treatment patterns and survival of cervical cancer in Sweden: A population-based Swedish Gynecologic Cancer Group Study

Maria Bjurberg [a,*], Erik Holmberg [b,c], Christer Borgfeldt [d], Angelique Flöter-Rådestad [e], Pernilla Dahm-Kähler [f], Elisabet Hjerpe [g], Thomas Högberg [h], Preben Kjølhede [i,j], Janusz Marcickiewicz [b,k], Per Rosenberg [l], Karin Stålberg [m], Bengt Tholander [n], Kristina Hellman [o], Elisabeth Åvall-Lundqvist [l]

[a] Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital, and Department of Clinical Sciences, Lund University, SE-22185 Lund, Sweden
[b] Region Västra Götaland, Regional Cancer Centre West, SE-41345 Gothenburg, Sweden
[c] Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, SE-41345 Gothenburg, Sweden
[d] Department of Obstetrics and Gynaecology, Skåne University Hospital and Lund University, SE-22185 Lund, Sweden
[e] Department of Women's and Children's Health, Division of Obstetrics and Gynaecology, Karolinska Institutet, Karolinska University Hospital, SE-17176 Stockholm, Sweden
[f] Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital, SE-41345 Gothenburg, Sweden
[g] Department of Gynaecology and Obstetrics, Visby Hospital, SE-62155 Visby, Sweden
[h] Department of Cancer Epidemiology, Lund University, SE-22100 Lund, Sweden
[i] Department of Obstetrics and Gynaecology, Linköping University Hospital, SE-58185 Linköping, Sweden
[j] Department of Clinical and Experimental Medicine, Linköping University, SE-58185 Linköping, Sweden
[k] Department of Obstetrics and Gynaecology, Halland Hospital, SE-43281 Varberg, Sweden
[l] Department of Oncology and Department of Clinical and Experimental Medicine, Linköping University, SE-58185 Linköping, Sweden
[m] Department of Women's and Children's Health, Uppsala University, SE-75185 Uppsala, Sweden
[n] Department of Oncology, Uppsala University Hospital, SE-75185 Uppsala, Sweden
[o] Department of Gynaecologic Cancer, Theme Cancer, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

HIGHLIGHTS

- In Sweden, the estimated age-standardised 5-year relative survival rate was 71% for cervical cancer diagnosed 2011–2015.
- Adherence to evidence-based guidelines was, in general, good.
- Survival was excellent for early stages of cervical cancer treated with surgery.
- To avoid combining surgery and radiotherapy, we suggest definitive chemoradiotherapy as primary treatment for stage IIA1.
- In this real-world setting, survival rates for stages III-IVA was lower than expected.

ARTICLE INFO

Article history:
Received 8 July 2019
Received in revised form
12 August 2019
Accepted 23 August 2019
Available online 30 August 2019

Keywords:
Cervical cancer
Survival
Treatment
Surgery
Radiotherapy

ABSTRACT

Objective: Survival in cervical cancer has improved little over the last decades. We aimed to elucidate primary treatment patterns and survival.

Methods: Population-based study of patients included in the Swedish Quality Registry for Gynecologic Cancer diagnosed 2011–2015. Main outcome was 5-year relative survival (RS). Age-standardised RS (AS-RS) was estimated for the total cohort and for the pooled study population of squamous, adenosquamous-, adenocarcinoma.

Results: Median follow-up time was 4.6 years. The study population consisted of 2141 patients; 97% of the 2212 patients in the total cohort and the 5-year AS-RS was 71% and 70%, respectively. RS stage IB1: surgery alone 95% vs. 72% for definitive chemoradiotherapy (CT-RT) ($p < 0.001$). In stage IIA1 74% had CT-RT, and 47% of operated patients received adjuvant (CT)-RT. RS stage IB2: surgically treated 81% (69% received adjuvant (CT)-RT) vs. 76% for (CT)-RT ($p = 0.73$). RS stage IIB: 77% for CT-RT + brachytherapy

* Corresponding author at: Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital, and Department of Clinical Sciences, Lund University, Lasarettsgatan 23, SE-22185 Lund, Sweden.
E-mail address: maria.bjurberg@med.lu.se (M. Bjurberg).

https://doi.org/10.1016/j.ygyno.2019.08.022

Data availability:
The datasets supporting the results of this study are not publicly available due to confidentiality reasons. Further information including the procedures to obtain and access data is available from the corresponding author.

(BT), 37% for RT + BT ($p = 0.045$) and 27% for RT-BT ($p < 0.001$). Stages III-IVA; <40% received CT-RT + BT, RS 45% vs. 18% for RT-BT (RR 4.1, $p < 0.001$). RS stage IVB 7%.

Conclusion: Primary treatment of cervical cancer in Sweden adhered to evidence-based standard of care. Areas of improvement include optimising treatment for stages III-IVA, and avoiding combining surgery and radiotherapy.

1. Introduction

Cervical cancer remains a major health problem worldwide with an estimated incidence of 530,000 new cases and 273,000 deaths annually [1,2]. In high-income countries such as Sweden, the incidence and mortality rates have substantially declined due to organised screening programmes [2,3]. However, global survival trends from population-based registry data for cervical cancer reveal only a slight improvement during the last decades [2,4,5]. In the 10 years between 1995 and 1999 and 2005–2009, the 5-year age-standardised relative survival (AS-RS) only increased from 65% to 68% [5]. Treatment advances reported in controlled clinical studies are only important if they can be translated into clinical practice and proven efficient in a real-world setting. Evidence-based guidelines for the management of cervical cancer are publicly available but data on to what extent these guidelines are followed as well as the survival outcome when generalising results from clinical trials to the population, are scarce.

Standard treatment of patients with early stage cervical cancer is radical hysterectomy and pelvic lymphadenectomy or definitive chemoradiotherapy (external beam radiotherapy, EBRT, with concomitant weekly cisplatin) including brachytherapy (BT) [6,7]. For microscopic disease without risk factors, conservative surgery is enough [8–10]. Neoadjuvant chemotherapy (NACT) is not recommended, but the focus of ongoing trials aiming to preserve fertility for stage IB tumours exceeding 2 cm [6,7,11]. The combination of surgery and radiotherapy should be limited, due to the risk of significant morbidity [6,12–14]. Definitive chemoradiation (CT-RT) is standard for patients with locally advanced cervical cancer, LACC [6,7,15,16]. BT is essential to include when delivering definitive CT-RT [17–20] but with improved techniques for delineation of target volumes and for the delivery of EBRT, the role of BT has been questioned [17,18,21].

We performed this population-based study to elucidate primary treatment patterns and survival outcome of patients diagnosed with squamous cell, adenocarcinoma and adenosquamous cervical cancer in Sweden 2011–2015. Personal identity numbers and official population-based registries in Sweden, covering all Swedish citizens, offer exceptionally good conditions for outcome studies.

2. Materials and methods

2.1. The Swedish Quality Registry for Gynecologic Cancer (SQRGC)

Reporting to the Swedish National Cancer Registry (NCR) is mandatory and has over 95% coverage for all malignant tumours of which 99% are histologically verified [22]. However, clinical data regarding treatment and follow-up is lacking. Hence, the SQRGC was established, with the registration of cervical cancer starting in 2011. The registration is web-based and includes information on patient and tumour characteristics, treatment details, and follow-up.

Reporting to the SQRGC is performed prospectively by all hospitals and clinics in the six Swedish Health Care regions. Quality control is continuously performed by registrars at the Regional Cancer Centres who monitor entered data. A manual with uniform definitions and criteria for each variable is easily accessible. Through the personal identification numbers allocated to all citizens in Sweden, the SQRGC continuously receives date of death from the Population Registry, the NCR, and the National Causes of Death Registry, enabling coverage control and life-long follow-up of patients. The validity of SQRGC data for ovarian and endometrial cancer has been assessed with 70–100% agreement between registered data and the original case files [23]. Patient consent is obtained for registration.

2.2. Study population

We used the SQRGC to identify eligible patients. The SQRGC captured between 97% and 100% of the cases in the NCR. Inclusion criteria were: age at least 18 years and histologically verified primary cancer of the cervix uteri (ICD-10 code C53) diagnosed from 1 January 2011–31 December 2015. All cases from the Northern Health Care region were excluded due to poor registration (33% of the cases), leaving an overall national coverage of 91%. Staging was performed according to the FIGO classification from 2009 [24]. Radiotherapy for cervical cancer in Sweden is centralised to seven university hospitals. All irradiated patients received photon beam EBRT and, in case of BT this was delivered with high-dose rate at all centres except one where pulse-dose rate was used.

Patients were followed until 15 March 2019 or to emigration or death, whichever came first. The ethical review board at Gothenburg University approved the study and ruled a separate study-specific consent as not needed (Dnr 794/14).

2.3. Statistics

The main outcome was relative survival (RS) measured from date of diagnosis to date of first event of death, emigration or end of follow-up (15th March 2019). The Pohar Perme method [25] was used to estimate the RS, which is a measure illustrating the excess mortality in a study population due to the disease, compared to the mortality in the general population. Age-standardised relative survival (AS-RS) for the total cohort and for the study population were estimated for international comparison but not for the different analysed subgroups due to small numbers. International Cancer Survival Standard 2 was used for weighting the age-specific survival rates. Mortality rates by gender, one-year age group and one-year calendar period for the general population in Sweden were used to estimate expected survival rates for the study cohorts. Relative risk of excess mortality (RR) between different groups was analysed by Poisson regression [26]. Observed survival was calculated by means of the actuarial estimator. A p-value of <0.05 was considered statistically significant. All statistical analyses were carried out with Stata/IC 15.1 for Mac (StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC).

3. Results

In total, 2212 women were diagnosed with cervical cancer of any histological subtype 2011–2015 and registered in the SQRGC. Mean

Table 1
Characteristics of the study population consisting of only squamous cell carcinoma, adenocarcinoma and adenosquamous cervical cancer.

Variable	Study population, n = 2141 (%)	Data on primary treatment, n = 2023 (%)
Age, years		
18–29	188 (8.8)	179 (8.8)
30–39	533 (24.9)	506 (25.0)
40–49	507 (23.7)	481 (23.8)
50–59	268 (12.5)	260 (12.8)
60–69	256 (12.0)	237 (11.7)
70–79	214 (10.0)	200 (9.9)
80–89	147 (6.9)	138 (6.8)
90–99	28 (1.3)	22 (1.1)
Median age (range)	46.4 (19–98)	46.3 (19–98)
Mean age (SD)	50.8 (17.6)	50.6 (17.5)
FIGO stage[a]		
IA1	438 (20.5)	417 (20.6)
IA2[b]	105 (4.9)	99 (4.9)
IB1[c]	680 (31.8)	658 (32.5)
IB2	113 (5.3)	109 (5.4)
IIA1	72 (3.4)	68 (3.4)
IIA2[d]	44 (2.1)	41 (2.0)
IIB[e]	306 (14.3)	281 (13.9)
IIIA	30 (1.4)	24 (1.2)
IIIB	172 (8.0)	163 (8.1)
IVA	69 (3.2)	62 (3.1)
IVB	64 (3.0)	63 (3.1)
X	48 (2.2)	38 (1.9)
Histology		
Squamous cell carcinoma	1561 (72.9)	1477 (73.0)
Adenocarcinoma	498 (23.3)	475 (23.5)
Adenosquamous carcinoma	82 (3.8)	71 (3.5)
Treatment intent		
Curative	1840 (85.9)	1840 (90.9)
Palliative	149 (7.0)	149 (7.4)
Undetermined	34 (1.6)	34 (1.7)
Missing	118 (5.5)	0
Follow-up, median (IQR), years	4.6 (0–8.2)	4.7 (0–8.2)

Abbreviations: FIGO, Federation International de Gynécologie et d'Obstétrique; SD, standard deviation; IQR, interquartile range.
[a] FIGO 2009.
[b] Including 1 case of stage IAX.
[c] Including 2 cases of stage IX.
[d] Including 1 case of stage IIAX.
[e] Including 2 cases of stage IIX.

age at diagnosis was 51 years. The histological subtypes were squamous cell carcinoma (71%), adenocarcinoma (23%), adenosquamous carcinoma (4%), neuroendocrine carcinoma (1%) and miscellaneous e.g. sarcoma, melanoma, lymphoma (2%).

In the study population of squamous cell, adenocarcinoma and adenosquamous cervical carcinoma (n = 2141), the median age was 46 years (range 19–98), see Table 1. At diagnosis, 34% were younger than 40 years. Median follow-up time was 4.6 years. Four patients emigrated and were lost to follow-up.

3.1. Treatment patterns

Data on primary treatment were registered for 2023 patients (96%), cf. Table 1. No primary treatment was given to 6% of the study population. Median age in this group was 81 years (range 24–97 years) and 63% had at least stage IIB. In 15% a FIGO stage could not be allocated.

3.1.1. Early stages of disease

Treatment patterns for early stages of cervical cancer are shown in Table 2. Primary surgery was performed in 98–100% of patients with stages IA1-IA2. In stage IB1, 588 (89%) patients were operated, 26% of them received postoperative adjuvant radiotherapy (ART). Surgery was performed in 22% of patients in stage IIA1, 47% received ART.

The most common indication for ART in stage IB1 and stage IIA1 was lymph node metastases (68% and 57%, respectively). Other indications were positive or close surgical margins, lymph vascular space invasion, pathological FIGO stage, depth of stromal invasion and tumour size. ART consisted predominantly of CT-RT. BT was included in 60–67% of stages IA1-IA2 and to a lesser extent in stages IB1 (47%) and IIA1 (33%). The median adjuvant EBRT dose was 46.8 Gy (range 21.0–62.4 Gy). For patients receiving adjuvant BT the median dose to the vaginal wall was 12.0 Gy (range 4.0–26.0 Gy) at 5 mm depth. For patients treated with definitive radiotherapy, CT-RT including BT was predominantly delivered (67% in stage IB1, 76% in stage IIA1).

3.1.2. Locally advanced cervical cancer (LACC)

Treatment patterns for LACC are shown in Table 3. In stage IB2, surgery was performed in 27% of the patients, of which 69% received ART. For irradiated patients, definitive CT-RT including BT was predominantly delivered in stages IB2-IIB but more seldom in stages IIIA-IVA.

The median EBRT dose was 47.0 Gy (range 27.0–66.0 Gy) and 46 Gy (range 7.2–80.1 Gy) for those who received (CT)-RT with or without BT, respectively. The median total BT dose was 24.0 Gy (range 4.0–64.0 Gy). The median total treatment time for patients receiving definitive radiotherapy with or without BT was 42 and 43 days respectively; 90% of patients finished RT within 53 and 55 days, respectively.

3.1.3. Metastatic disease

Treatment modalities for the 63 patients with stage IVB varied. (CT)-RT ± BT was delivered to 29%, chemotherapy alone to 24%, 13% underwent surgery with or without ART, and 10% received neo-adjuvant CT-RT, whereas 25% did not receive any anti-tumour treatment.

3.2. Survival outcomes

The 5-year OS, RS, and AS-RS rates for all cervical cancer patients (n = 2212) were 73% (95% CI 71%–75%), 75% (95% CI 73%–77%), and 70% (95% CI 67%–72%), respectively. The RS including all stages varied with histology as demonstrated in Fig. 1A. The 5-year RS for adenocarcinomas (80%, p = 0.15) or adenosquamous carcinomas (72%, p = 0.36) did not significantly differ compared to for squamous cell carcinoma (76%), neither in the entire cohort nor in the cohort of stage IIB in which all had received definitive radiation. The 5-year OS, RS, AS-RS and RR in relation to histology are shown in Supplementary Table 1A.

3.2.1. Survival outcome in the study population

The 5-year OS, RS, and AS-RS rates for the study population were 74% (95% CI 72%–76%), 76% (95% CI 75%–79%), and 71% (95% CI 68%–73%), respectively. The RS by FIGO stage is shown in Fig. 1B. The 5-year RS per stage was for: IA1 98%, IA2 98%, IB1 92%, IB2 75%, IIA1 72%, IIA2 73%, IIB 66%, IIIA 24%, IIIB 32%, IVA 24%, and for stage IVB 7%. The 5-year stage-specific OS, RS, AS-RS and RR are shown in Supplementary Table 1B.

3.2.2. FIGO stages IA1-IB1 in relation to treatment

Fig. 2 illustrates the RS for patients with early stages of cervical cancer in relation to treatment. In patients with stages IA1-IB1 treated with surgery alone (n = 934) the 5-year RS for stage IA1 was significantly higher (99%, 95% CI 96%–100%) compared to that of stage IB1 (95%, 95% CI 92%–97%, RR 5.5, p = 0.03), see Fig. 2A, and Supplementary Table 2A.

Table 2
Treatment patterns for early stages of squamous cell, adenocarcinoma, and adenosquamous cervical cancer.

Treatment	IA1 n = 417	IA2[a] n = 99	IB1[b] n = 658	IIA1 n = 68
Primary surgery, n (%)	410 (98.3)	99 (100.0)	588 (89.4)	15 (22.0)
Type of surgical procedure, n (%)	269 (65.6)	78 (78.8)	467 (79.4)	14 (93.3)
Conisation	97 (36.1)	3 (3.8)	4 (0.9)	0
Simple hysterectomy	150 (55.8)	17 (21.8)	29 (6.2)	3 (21.4)
Trachelectomy + lymphadenectomy	1 (0.4)	12 (15.4)	32 (6.9)	0
Radical hysterectomy + lymphadenectomy	21 (7.8)	46 (59.0)	402 (86.1)	11 (78.6)
Missing information	141 (34.4)	21 (21.2)	121 (20.6)	1 (6.7)
Primary surgery only	405 (98.8)	95 (96.0)	434 (73.8)	8 (53.3)
Postoperative adjuvant radiotherapy, n (%)	5 (1.2)	4 (4.0)	154 (26.2)	7 (46.7)
Chemoradiotherapy	5 (100.0)	3 (75.0)	134 (87.0)	6 (85.7)
With brachytherapy	3	2	63	2
Without brachytherapy	2	1	71	4
External beam radiotherapy	0	1 (25.0)	20 ((13.0)	1 (14.3)
With brachytherapy	0	1	10	1
Without brachytherapy	0	0	10	0
Neoadjuvant therapy before surgery, n (%)	0	0	0	1 (1.5)
Chemoradiotherapy followed by surgery	0	0	0	1 (100.0)
Definitive radiotherapy, n (%)	2 (0.5)	0	63 (9.6)	50 (73.5)
Chemoradiotherapy, n (%)	2 (100.0)	0	45 (71.4)	41 (82.0)
With brachytherapy	2	0	42	38
Without brachytherapy	0	0	3	3
External beam radiotherapy, n (%)	0	0	18 (28.6)	9 (18.0)
With brachytherapy	0	0	13	5
Without brachytherapy	0	0	5	4
Neoadjuvant chemotherapy before radiotherapy[c], n (%)	0	0	0	1 (1.5)
No treatment, n (%)	5 (1.2)	0	7 (1.1)	1 (1.5)

[a] Including 1 case of stage IAX.
[b] Including 2 cases of stage IX.
[c] With or without brachyterapy, and/or concurrent chemotherapy.

The 5-year RS for patients with stage 1B1 treated with only surgery was significantly higher than for those treated with combined surgery and ART (95%, 95% CI 92%–97% vs 87%, 95% CI 79%–93%, RR 2.3, $p = 0.03$) and for patients receiving definitive (CT)-RT ± BT (72%, 95% CI 54%–84%, RR 5.8, $p < 0.001$), Fig. 2B. The 5-year OS and RS rates for early stage disease with 95% CI and RR are shown in Supplementary Tables 2A-2B.

3.2.3. FIGO stages IB2-IVA in relation to treatment

In stage IB2, there was no significant difference in 5-year RS between patients treated with surgery ± ART (81%, 95% CI 60%–90%) and patients treated with definitive (CT)-RT ± BT (76%, 95% CI 63%–85%), Fig. 3A and Supplementary Table 3A. The 5-year RS for stages IIB-IVA treated with definitive (CT)-RT ± BT is demonstrated in Fig. 3B and C. Patients in stage IIB treated with definitive CT-RT

Table 3
Treatment patterns for locally advanced stages of squamous cell, adenocarcinoma and adenosquamous cervical cancer.

Treatment	IB2 n = 109	IIA2[a] n = 41	IIB[b] n = 281	IIIA n = 24	IIIB n = 163	IVA n = 62
Primary surgery, n (%)	29 (26.6)	2 (4.9)	12 (4.3)	0	4 (2.5)	4 (6.5)
Type of surgical procedure, n (%)	17 (58.6)	2 (100.0)	6 (50.0)	0	2 (50.0)	3 (75.0)
Simple hysterectomy + lymphadenectomy	7 (41.2)	2 (100.0)	4 (66.7)	0	1 (50.0)	3 (100.0)
Trachelectomy + lymphadenectomy	0	0	0	0	0	0
Radical hysterectomy + lymphadenectomy	10 (58.8)	0	2 (33.3)	0	1 (50.0)	0
Missing information	12 (41.4)	0	6 (50.0)	0	2 (50.0)	0
Primary surgery only, n (%)	9 (31.0)	1 (50.0)	3 (25.0)	0	0	1 (25.0)
Postoperative adjuvant radiotherapy, n (%)	20 (69.0)	1 (50.0)	9 (75.0)	0	4 (100.0)	3 (75.0)
Chemoradiotherapy	15 (75.0)	1 (100.0)	7 (77.8)	0	2 (50.0)	1 (33.3)
With brachytherapy	5	1	2	0	0	1
Without brachytherapy	10	0	5	0	2	0
External beam radiotherapy	5 (25.0)	0	2 (22.2)	0	2 (50.0)	2 (66.7)
With brachytherapy	1	0	2	0	0	0
Without brachytherapy	4	0	0	0	2	2
Neoadjuvant therapy followed by surgery, n (%)	1 (0.9)	2 (4.9)	1 (0.4)	0	0	0
Chemotherapy followed by surgery	1 (100.0)	2 (100.0)	1 (100.0)	0	0	0
Definitive radiotherapy, n (%)	73 (67.0)	34 (82.9)	252 (89.7)	22 (91.7)	134 (82.2)	43 (69.4)
Chemoradiotherapy, no. (%)	69 (94.5)	31 (91.2)	200 (79.4)	11 (50.0)	80 (59.7)	21 (48.8)
With brachytherapy	66	30	180	8	52	14
Without brachytherapy	3	1	20	3	28	7
External beam radiotherapy, no. (%)	4 (5.5)	3 (8.8)	52 (20.6)	11 (50.0)	54 (40.3)	22 (51.2)
With brachytherapy	1	1	26	3	15	1
Without brachytherapy	3	2	26	8	39	21
Neoadjuvant chemotherapy followed by radiotherapy[c], n (%)	3 (2.8)	0	6 (2.1)	0	7 (4.3)	4 (6.5)
Primary chemotherapy alone, n (%)	0	2 (4.9)	2 (0.7)	0	2 (1.2)	3 (4.8)
No treatment, n (%)	3 (2.8)	1 (2.4)	8 (2.8)	2 (8.3)	16 (9.8)	8 (12.9)

[a] Including 1 case of stage IIAX.
[b] Including 2 cases of stage IIX.
[c] With or without brachyterapy, and/or concurrent chemotherapy.

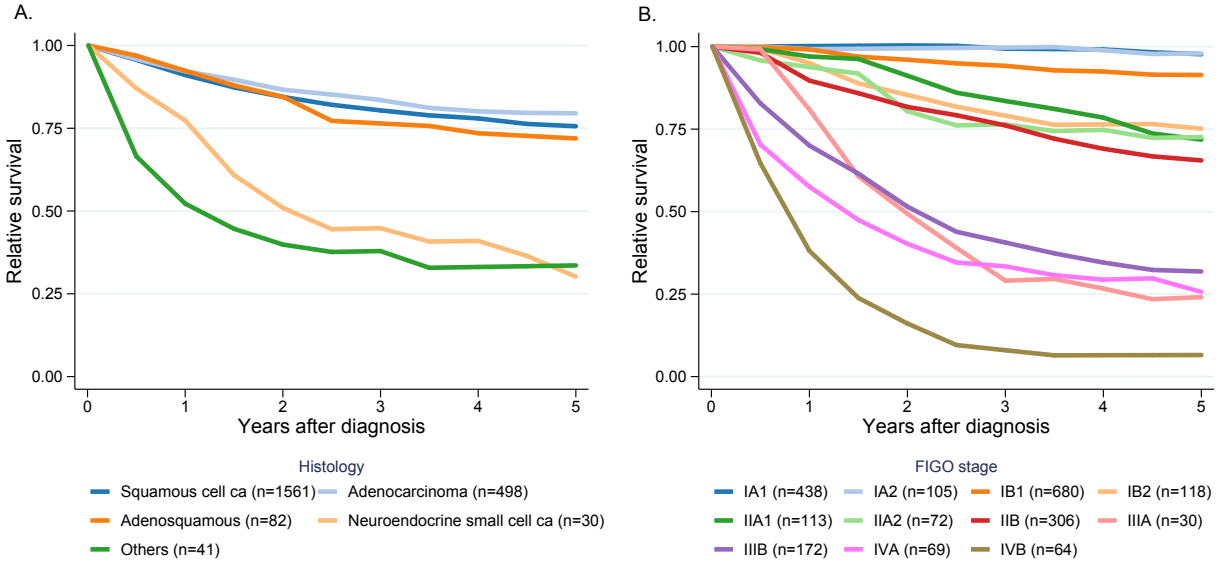

Fig. 1. Relative survival (RS) for women diagnosed with cervical cancer 2011–2015 in five out of six health care regions in Sweden A) by histology (n = 2212), and B) by stage (stage X not included) for the study population of women with squamous cell, adenocarcinoma, and adenosquamous cell carcinoma.

and BT had a 5-year RS of 77% (95% CI 70%–83%) which was significantly higher than for patients treated with EBRT with BT (37%, 95% CI 14%-60%; RR 2.3, p = 0.05) or with EBRT alone (27% 95% CI 6%–55%, RR 5.2, p < 0.001). No significant difference was found when comparing CT-RT with or without brachytherapy in stage IIB (73%, 95% CI 46%–88%, RR 1.4, p = 0.53), Supplementary Table 3B.

For patients in stage III treated with CT-RT and BT the 5-year OS and RS rates were 45% (95% CI 31%–58%) and 47% (95% CI 32%–60%), respectively. In stages IIIA-IVA, the 5-year RS was 45% (95% CI 30%–60%) for patients treated with CT-RT and BT which was significantly higher than that of patients treated with EBRT alone (18%, 95% CI 8%–30%, RR 4.1, p < 0.001). Those treated with EBRT and BT had a 5-year RS of 42% (95% CI 10%–73%), and patients treated with CT-RT without BT had a 5-year RS rate of 41% (95% CI 23%–58%). The 5-year OS and RS rates for LACC with 95% CI and RR are shown in Supplementary Table 3A-3C.

4. Discussion

In this population-based study, covering >90% of the Swedish female population, we report details on primary treatment patterns and survival rates for patients diagnosed 2011–2015 with cervical cancer. The estimated age-standardised 5-year relative survival rate was only 71% despite the exclusion of the more aggressive and uncommon tumour types and that most patients were diagnosed in stages IA1-IB1. Surgically treated patients with early stage cervical cancer had excellent survival rates. For the 10% of stage IB1 patients treated with definitive (chemo)radiotherapy, the 5-year survival rates were significantly poorer than for the group treated with surgery alone, with a difference of 22% in RS. For locally advanced cervical cancer, standard treatment with chemoradiation including brachytherapy was delivered to over 70% in stages IB2-IIB but to <40% of patients in stages IIIA-IVA. The 5-year relative survival rate of 47% for patients in stage III treated with chemoradiotherapy and brachytherapy was lower than reported from clinical trials [27,28]. We also observed a frequent use of adjuvant (chemo)radiotherapy for surgically treated patients in stages IIA1 and IB2.

The patients in our study were diagnosed at a younger age and in an earlier stage of disease than similar cohorts previously reported [29,30]. These differences are most likely attributable to the effectiveness of the organised screening programme in Sweden. The observed differences also underscores the importance of age-standardisation when comparing survival rates between countries [5].

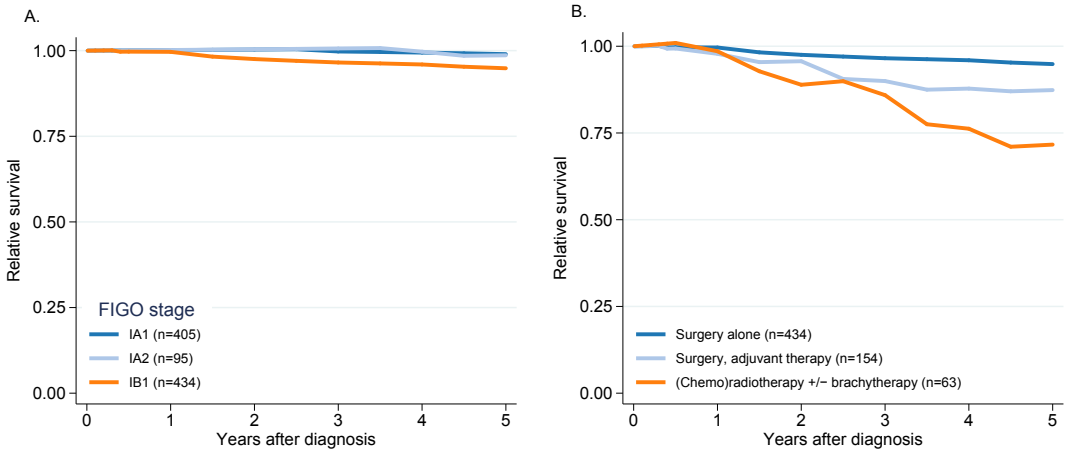

Fig. 2. Relative survival (RS) for the study population of squamous cell, adenocarcinoma and adenosquamous carcinoma stage IA1-IB1 of the uterine cervix. A) RS stage IA1-IB1 with surgery as only treatment modality. B) RS stage IB1 by treatment modality.

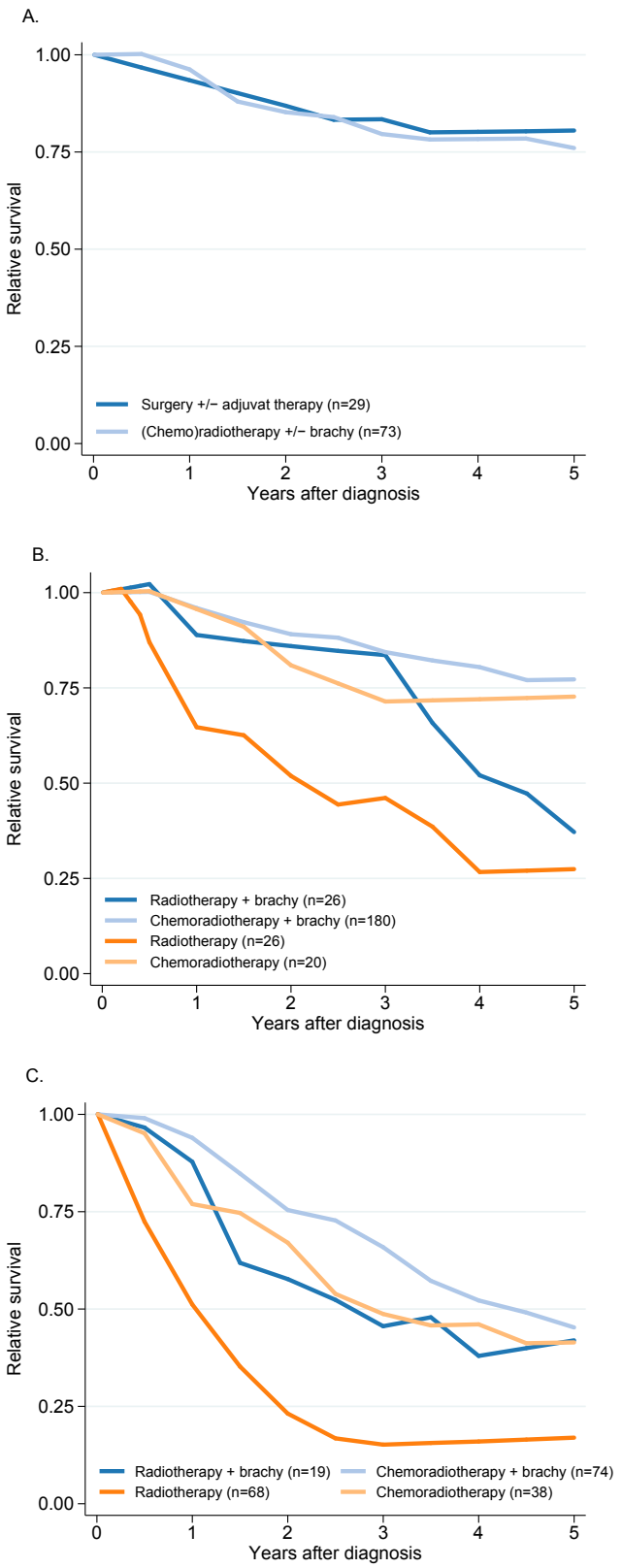

Fig. 3. Relative survival (RS) for the study population of squamous cell, adenocarcinoma and adenosquamous cervical cancer with locally advanced disease. A) RS stage IB2 by treatment modality. B) RS stage IIB treated with definitive (chemo)radiotherapy ± brachytherapy. C) RS stage III-IVA treated with definitive (chemo)radiotherapy ± brachytherapy.

Our excellent treatment results for surgically treated patients with stages IA1-IB1 are in line with those reported by others [2,29]. The objective in early stage of cervical cancer is therefore to reduce the risk for treatment-related morbidity e.g. offering fertility-sparing treatment. Hence, conisation is standard of care in stage IA1 [8–10], but in our study only one third of patients were treated accordingly. Instead simple hysterectomy was frequently performed. Although there is no evidence for improved survival after hysterectomy compared to after conisation, follow-up schemes differ, which may have favoured hysterectomy, especially among postmenopausal women. In the on-going randomised SHAPE trial (NCT01658930) radical hysterectomy is compared to simple hysterectomy with pelvic node dissection, including patients with stages IA2-IB1 with <50% stromal invasion. In our study approximately one fifth of the patients in stage IA2 had simple hysterectomy, which contrasted with current guidelines. The CONTESSA/NEOCON-F trials explore NACT and conservative surgery in order to preserve fertility for patients in stage IB1 with tumours 2–4 cm [11]. In our population-based study, only one patient received NACT followed by surgery.

Dual-modality treatment with surgery followed by ART in early stage cervical cancer causes more side effects than either modality on its own [6,13,31]. A challenge in the management of stage IB1 is to avoid this added toxicity by using a meticulous staging procedure in order to allocate patients to the optimal treatment strategy. In the literature the reported rates of ART after radical hysterectomy and pelvic lymphadenectomy for early stages vary between 10 and 64% [12,14,29,32]. In our study, 26% of operated stage IB1 patients received ART. The benefit of ART for node-negative patients with "intermediate" risk factors as shown in GOG 92 [33], has been challenged by a retrospective cohort study showing that excellent oncological outcome can be achieved with surgery alone [34]. If improved surgical techniques, together with more accurate preoperative and pathological staging, can lead to non-inferior results compared to what is seen for dual-modality treatment in patients with node-negative stage IB tumours with intermediate risk factors, needs to be evaluated in a randomised trial before changing practice.

The more frequent use of including BT in ART for stages IA1-IA2 (60–67%) compared to for stage IB1 (47%) is probably due to that a vaginal cuff is not routinely removed in the lower stages and thus a positive or close surgical margin would be more common in the earlier stages.

The 5-year RS for stage IB1 patients treated with definitive (CT)-RT was significantly lower (72%) compared to that of patients treated with surgery alone (95%). This small group of patients (n = 63) includes women unfit for surgery and those with pelvic lymph node metastases where surgery was aborted. Interpretation should therefore be cautious.

Stage IIA1 accounts for a small percentage of early stage cervical cancer and thus published reports on survival rates are limited. Many international guidelines [6,7,35] recommend surgical treatment although definitive (CT)-RT may be an option. In line with our results, a retrospective cohort study from Israel reported a high rate of ART for surgically treated patients [36]. We therefore propose that CT-RT with BT should be the preferred treatment for stage IIA1.

We did not find a significant difference in RS for patients with stage IB2 in relation to treatment modality (surgery 81% vs. (CT)-RT 76%, p = 0.73). NACT followed by surgery has been compared to definitive chemoradiation in two randomised phase III trials [37,38]. The study by Gupta et al. included 635 patients with squamous cervical cancer in stages IB2, IIA and IIB. The 5-year disease-free survival was significantly superior for cisplatin-based CT-RT compared to NACT followed by surgery, but no difference was found in OS. The reported OS of 75% for CT-RT was in accordance with our findings of 75% in stages IB2 and IIB treated with definitive CT-RT. In the second randomised trial, EORTC 55954, including 626 patients IB2, IIA and IIB also other histological types were eligible i.e. adenosquamous or adenocarcinoma. In their

intention-to-treat analysis, progression-free survival was significantly longer for definitive CT-RT compared to NACT followed by surgery, while no difference in OS was reported [38]. In our study, more than one fourth of patients with stage IB2 were operated, 69% of them also received ART. Only one patient received NACT. To avoid dual-modality treatment, definitive chemoradiation should be advocated for stage IB2.

In definitive radiotherapy, the importance of adding BT has been questioned since the introduction of more precise methods of EBRT delivery [17,18,21]. However, image-guided adaptive BT has shown to be important in improving the survival and local control rates of cervical cancer as well as in lowering the incidence of side effects [19,39–41]. We observed a higher RS rate for patients with stages IIB-IVA who were given BT as part of definitive CT-RT compared to for those who did not receive BT. These findings are in concurrence with the results presented by Han et al. [17]. In their report of 7359 women treated with definitive EBRT for cervical cancer 1988–2009 in the US identified in the SEER database the authors found that BT was independently associated with improved survival and reported OS to drop from 58.2% to 46.2% ($p < 0.001$) when BT was not delivered. More recent data from a study presented by Gill et al. confirmed the observed declination in the use of BT in the US and the following poorer survival rates [42]. Using the National Cancer Database the authors identified 7654 women with cervical cancer FIGO stage IIB-IVA treated with definitive radiation 2004–2011. Patient who did not receive BT had a significantly poorer outcome even if an EBRT boost was given [42]. Our data supports to the use of BT as a critical treatment modality in the curation of LACC.

Our study confirms the advantage of CT-RT over RT alone in LACC. The addition of concomitant chemotherapy has been shown to improve survival rates in all stages of LACC compared to radiotherapy alone [27,28]. In a population-based setting as in our study, the absolute difference between CT-RT and RT alone is difficult to estimate without adjusting for prognostic factors which was not possible due to lack of data and small number of patients. Our results of CT-RT with BT for stage III patients showed an OS of 45% which was inferior to the outcome reported in the phase III trial by Shrivastava et al. In their study of 850 women with stage III squamous cell carcinoma and median age 49 years, the 5-year OS for patients treated with CT-RT was 54% [28]. When generalising results from randomised trials into the real world, survival rates may differ due to e.g. older age and comorbidities. However, the poorer results in our study need to be interpreted with caution due to small number of patients as indicated by the wide 95% CI of 28%–57%. It is less likely that we have delivered poor quality of CT-RT, since the results in earlier stages are in line with those reported by others, and the time limits for radiotherapy were well-kept. Surprisingly, <40% of patients with stages III-IVA received CT-RT with BT. Further in-depth studies are needed to explore the reasons for not providing standard CT-RT to more patients. The fear of developing treatment-related toxicities from CT-RT with curative intent in elderly patients may have contributed [43].

For LACC treated with definitive radiotherapy, adenocarcinoma and adenosquamous carcinoma has been reported to be independent poor prognostic factors in a large cohort of 8751 patients from the SEER database [44]. This could not be confirmed in our study. However, the lack of difference could possibly be obscured by the smaller size of our study population. The potential influence of histological types needs to be validated in a prospective setting with standardised radiotherapy.

The 5-year RS for metastatic disease, stage IVB, was only 7% in our study, but is in accordance with the findings from a US study of the SEER database comparing the RS of 5414 patients diagnosed with stage IV disease between 1983 and 2009 [30]. One fourth of the patients with metastatic disease in our study did not receive any treatment.

New treatment strategies are urgently needed for advanced cervical cancer. The addition of bevacizumab to chemotherapy has been reported to improve survival compared to chemotherapy alone and is now implemented in standard of care [45]. The addition of chemotherapy to CT-RT either before (INTERLACE trial, NCT01566240) or after (OUTBACK trial, NCT01414608) is currently being explored in phase III trials. New concepts with vaccines targeting HPV-E7 (AIM2CERV trial, NCT02853604), other immunotherapies such as immune check-point inhibitors, and PARP-inhibitors are evaluated in ongoing or planned clinical trials. Although the results of these trials are eagerly awaited, from a population-based point of view, preventive measures with HPV vaccination and organised screening have the best ability to decrease mortality and improve survival rates for cervical cancer.

The main strengths of our study are the unselected population-based setting, covering over 90% of the Swedish population, and the data quality and completeness. There were few missing data except for type of surgical procedure in early stages. Another strength is the SQRGC linkage to other official databases which ascertains the vital status for registered patients. To enable international comparison, we estimated age-standardised relative survival when applicable, but RS and OS were also estimated. Although reports from larger population-based cohorts of cervical cancer patients than ours exist, we are not aware of any other study providing as much details on primary treatment.

In conclusion, our study illustrates the importance of population-based outcome studies with high coverage. Compared to the reported estimated RS for cervical cancer patients diagnosed 2005–2009 in Sweden [5], the survival rates 10 years later show no improvement. New treatment strategies are highly needed to improve survival but also to reduce overtreatment and long-term toxicity. Considering our findings, we propose definitive CT-RT with BT as primary choice of treatment for stage IIA1. In general, primary treatment of cervical cancer patients in Sweden adhered to evidence-based standard of care but areas of improvement were identified and include optimising treatment for stages III-IVA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.08.022.

Funding

The Swedish Cancer Society.

Authors' contributions

All authors designed the study and analysed the results.
EH extracted data and made statistical analyses.
MB and EÅL wrote the manuscript.
All authors critically revised the manuscript, approved the final version and are accountable for all aspects of the work.

Declaration of competing interest

The authors declare no conflict of interest.

References

[1] L.A. Torre, R.L. Siegel, E.M. Ward, A. Jemal, Global cancer incidence and mortality rates and trends–an update, Cancer Epidemiol. Biomark. Prev. 25 (1) (2016) 16–27.
[2] IARC, GLOBOCAN, URL, www-dep.iarc.fr, IARC, (accessed May 19 2019).
[3] E. Laara, N.E. Day, M. Hakama, Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes, Lancet 1 (8544) (1987) 1247–1249.
[4] A. Klint, L. Tryggvadottir, F. Bray, M. Gislum, T. Hakulinen, H.H. Storm, et al., Trends in the survival of patients diagnosed with cancer in female genital organs in the Nordic countries 1964-2003 followed up to the end of 2006, Acta Oncol. 49 (5) (2010) 632–643.

[5] C. Allemani, H.K. Weir, H. Carreira, R. Harewood, D. Spika, X.S. Wang, et al., Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2), Lancet 385 (9972) (2015) 977–1010.
[6] N. Bhatla, D. Aoki, D.N. Sharma, R. Sankaranarayanan, Cancer of the cervix uteri, Int. J. Gynaecol. Obstet. 143 (Suppl. 2) (2018) 22–36.
[7] D. Cibula, R. Potter, F. Planchamp, E. Avall-Lundqvist, D. Fischerova, C. Haie Meder, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer, Radiother. Oncol. 127 (3) (2018) 404–416.
[8] Q. Qian, J. Yang, D. Cao, Y. You, J. Chen, K. Shen, Analysis of treatment modalities and prognosis on microinvasive cervical cancer: a 10-year cohort study in China, J. Gynecol. Oncol. 25 (4) (2014) 293–300.
[9] L. Spoozak, S.N. Lewin, W.M. Burke, I. Deutsch, X. Sun, T.J. Herzog, et al., Microinvasive adenocarcinoma of the cervix, Am. J. Obstet. Gynecol. 206 (1) (2012) (80.e1-6).
[10] J.D. Wright, R. NathavithArana, S.N. Lewin, X. Sun, I. Deutsch, W.M. Burke, et al., Fertility-conserving surgery for young women with stage IA1 cervical cancer: safety and access, Obstet. Gynecol. 115 (3) (2010) 585–590.
[11] M. Plante, N. van Trommel, S. Lheureux, A.M. Oza, L. Wang, K. Sikorska, et al., FIGO 2018 stage IB2 (2-4 cm) cervical cancer treated with neo-adjuvant chemotherapy followed by fertility sparing surgery (CONTESSA); neo-adjuvant chemotherapy and conservative surgery in cervical cancer to preserve fertility (NEOCON-F). A PMHC, DGOG, GCIG/CCRN and multicenter study, Int. J. Gynecol. Cancer (2019), https://doi.org/10.1136/ijgc-2019-000398 e-pub ahead of print 19 May2019.
[12] O. Gemer, O. Lavie, M. Gdalevich, R. Eitan, E. Mamanov, B. Piura, et al., Evaluation of clinical and pathologic risk factors may reduce the rate of multimodality treatment of early cervical cancer, Am. J. Clin. Oncol. 39 (1) (2016) 37–42.
[13] F. Landoni, A. Colombo, R. Milani, F. Placa, V. Zanagnolo, C. Mangioni, Randomized study between radical surgery and radiotherapy for the treatment of stage IB-IIA cervical cancer: 20-year update, J. Gynecol. Oncol. 28 (3) (2017) e34.
[14] F. Landoni, A. Maneo, A. Colombo, F. Placa, R. Milani, P. Perego, et al., Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer, Lancet 350 (9077) (1997) 535–540.
[15] P.G. Rose, B.N. Bundy, E.B. Watkins, J.T. Thigpen, G. Deppe, M.A. Maiman, et al., Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer, N. Engl. J. Med. 340 (15) (1999) 1144–1153.
[16] C.W. Whitney, W. Sause, B.N. Bundy, J.H. Malfetano, E.V. Hannigan, W.C. Fowler Jr., et al., Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study, J. Clin. Oncol. 17 (5) (1999) 1339–1348.
[17] K. Han, M. Milosevic, A. Fyles, M. Pintilie, A.N. Viswanathan, Trends in the utilization of brachytherapy in cervical cancer in the United States, Int. J. Radiat. Oncol. Biol. Phys. 87 (1) (2013) 111–119.
[18] D.G. Petereit, S.J. Frank, A.N. Viswanathan, B. Erickson, P. Eifel, P.L. Nguyen, et al., Brachytherapy: where has it gone? J. Clin. Oncol. 33 (9) (2015) 980–982.
[19] A. Sturdza, R. Potter, L.U. Fokdal, C. Haie-Meder, L.T. Tan, R. Mazeron, et al., Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study, Radiother. Oncol. 120 (3) (2016) 428–433.
[20] K. Tanderup, N. Nesvacil, R. Potter, C. Kirisits, Uncertainties in image guided adaptive cervix cancer brachytherapy: impact on planning and prescription, Radiother. Oncol. 107 (1) (2013) 1–5.
[21] K. Tanderup, P.J. Eifel, C.M. Yashar, R. Potter, P.W. Grigsby, Curative radiation therapy for locally advanced cervical cancer: brachytherapy is NOT optional, Int. J. Radiat. Oncol. Biol. Phys. 88 (3) (2014) 537–539.
[22] L. Barlow, K. Westergren, L. Holmberg, M. Talback, The completeness of the Swedish Cancer register: a sample survey for year 1998, Acta Oncol. 48 (1) (2009) 27–33.
[23] P. Rosenberg, P. Kjolhede, C. Staf, M. Bjurberg, C. Borgfeldt, P. Dahm-Kahler, et al., Data quality in the Swedish Quality Register of Gynecologic Cancer - a Swedish Gynecologic Cancer Group (SweGCG) study, Acta Oncol. 57 (3) (2018) 346–353.
[24] S. Pecorelli, L. Zigliani, F. Odicino, Revised FIGO staging for carcinoma of the cervix, Int. J. Gynaecol. Obstet. 105 (2) (2009) 107–108.
[25] M.P. Perme, J. Stare, J. Esteve, On estimation in relative survival, Biometrics 68 (1) (2012) 113–120.
[26] P.W. Dickman, A. Sloggett, M. Hills, T. Hakulinen, Regression models for relative survival, Stat. Med. 23 (1) (2004) 51–64.
[27] C. Vale, J.F. Tierney, L.A. Stewart, M. Brady, K. Dinshaw, A. Jakobsen, et al., Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials, J. Clin. Oncol. 26 (35) (2008) 5802–5812.
[28] S. Shrivastava, U. Mahantshetty, R. Engineer, S. Chopra, R. Hawaldar, V. Hande, et al., Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: a randomized clinical trial, JAMA oncology 4 (4) (2018) 506–513.
[29] M.A. Quinn, J.L. Benedet, F. Odicino, P. Maisonneuve, U. Beller, W.T. Creasman, et al., Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological cancer, Int. J. Gynaecol. Obstet. 95 (Suppl. 1) (2006) S43–S103.
[30] J.D. Wright, L. Chen, A.I. Tergas, W.M. Burke, J.Y. Hou, A.I. Neugut, et al., Population-level trends in relative survival for cervical cancer, Am. J. Obstet. Gynecol. 213 (5) (2015) (670.e1-7).
[31] Q.D. Pieterse, G.G. Kenter, C.P. Maas, C.D. de Kroon, C.L. Creutzberg, J.B. Trimbos, et al., Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: longitudinal prospective cohort study, Int. J. Gynecol. Cancer 23 (9) (2013) 1717–1725.
[32] A. Ayhan, R.A. Al, C. Baykal, E. Demirtas, A. Ayhan, K. Yuce, Prognostic factors in FIGO stage IB cervical cancer without lymph node metastasis and the role of adjuvant radiotherapy after radical hysterectomy, Int. J. Gynecol. Cancer 14 (2) (2004) 286–292.
[33] A. Sedlis, B.N. Bundy, M.Z. Rotman, S.S. Lentz, L.I. Muderspach, R.J. Zaino, A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study, Gynecol. Oncol. 73 (2) (1999) 177–183.
[34] D. Cibula, N.R. Abu-Rustum, D. Fischerova, S. Pather, K. Lavigne, J. Slama, et al., Surgical treatment of "intermediate risk" lymph node negative cervical cancer patients without adjuvant radiotherapy-a retrospective cohort study and review of the literature, Gynecol. Oncol. 151 (3) (2018) 438–443.
[35] W.J. Koh, B.E. Greer, N.R. Abu-Rustum, S.M. Apte, S.M. Campos, K.R. Cho, et al., Cervical cancer, version 2.2015, J. Natl. Compr. Cancer Netw. 13 (4) (2015) 395–404.
[36] Y. Yagur, O. Weitzner, O. Gemer, O. Lavie, U. Beller, I. Bruchim, et al., Postoperative radiation rates in stage IIA1 cervical cancer: is surgical treatment justified? An Israeli Gynecologic Oncology Group Study, Gynecol. Oncol. 150 (2) (2018) 288–292.
[37] S. Gupta, A. Maheshwari, P. Parab, U. Mahantshetty, R. Hawaldar, S. Sastri Chopra, et al., Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial, J. Clin. Oncol. 36 (16) (2018) 1548–1555.
[38] Kenter G, Greggi S, Vergote I, Katsaros D, Kobierski FJ, Massuger L, et al. Results from neoadjuvant chemotherapy followed by surgery compared to chemoradiation for stage Ib2-IIb cervical cancer EORTC GCG 55994. J. Clin. Oncol. 2019 (abstr 5503) ASCO; Chicago, USA.
[39] C. Haie-Meder, R. Potter, E. Van Limbergen, E. Briot, M. De Brabandere, J. Dimopoulos, et al., Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV, Radiother. Oncol. 74 (3) (2005) 235–245.
[40] K. Kirchheiner, R.A. Nout, K. Tanderup, J.C. Lindegaard, H. Westerveld, C. Haie-Meder, et al., Manifestation pattern of early-late vaginal morbidity after definitive radiation (chemo)therapy and image-guided adaptive brachytherapy for locally advanced cervical cancer: an analysis from the EMBRACE study, Int. J. Radiat. Oncol. Biol. Phys. 89 (1) (2014) 88–95.
[41] J.C. Lindegaard, L.U. Fokdal, S.K. Nielsen, J. Juul-Christensen, K. Tanderup, MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective, Acta Oncol. 52 (7) (2013) 1510–1519.
[42] B.S. Gill, J.F. Lin, T.C. Krivak, P. Sukumvanich, R.A. Laskey, M.S. Ross, et al., National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements, Int. J. Radiat. Oncol. Biol. Phys. 90 (5) (2014) 1083–1090.
[43] M. Hata, Radiation therapy for elderly patients with uterine cervical cancer: feasibility of curative treatment, Int. J. Gynecol. Cancer 29 (3) (2019) 622–629.
[44] J. Zhou, S.G. Wu, J.Y. Sun, F.Y. Li, H.X. Lin, Q.H. Chen, et al., Comparison of clinical outcomes of squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma of the uterine cervix after definitive radiotherapy: a population-based analysis, J. Cancer Res. Clin. Oncol. 143 (1) (2017) 115–122.
[45] K.S. Tewari, M.W. Sill, R.T. Penson, H. Huang, L.M. Ramondetta, L.M. Landrum, et al., Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240), Lancet 390 (10103) (2017) 1654–1663.