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Original Research

No improvement in survival of older women with cervical cancer—A nationwide study

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Abstract ***Aim:*** This study aims to report trends in primary treatment and survival in cervical cancer (CC) to identify opportunities to improve clinical practice and disease outcome.
Methods: Patients diagnosed with CC between 1989 and 2018 were identified from the Netherlands Cancer Registry ($N = 21{,}644$). Trends in primary treatment and 5-year relative survival were analysed with the Cochran-Armitage trend test and multivariable Poisson regression, respectively.
Results: In early CC, surgery remains the preferred treatment for ages 15–74. Overall, it was applied more often in younger than in older patients (92% in 15–44; 64% in 65–74). For 75+, surgery use was stable over time (38%–41%, $p = 0.368$), while administration of radiotherapy decreased (57%–29%, $p < 0.001$). In locally advanced CC, chemoradiation use increased over time (5%–65%, $p < 0.001$). It was applied least often for 75+, in which radiotherapy remains most common (54% in 2014–2018). In metastatic CC, chemotherapy use increased over time (11%–28%, $p < 0.001$), but varied across age groups (6%–40% in 2014–2018). In patients treated with primary chemoradiation, regardless of stage, brachytherapy use increased over time ($p \leq 0.001$). Full cohort 5-year survival increased from 68% to 74% (relative excess risk 0.55; 95% confidence interval [0.50–0.62]). Increases were most significant in locally advanced CC (38%–60%; 0.55 [0.47–0.65]). Survival remained stable in 75+ (38%–34%; 0.82 [0.66–1.02]).

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Conclusion: Relative survival for cervical cancer increased over the last three decades. The proportion of older patients receiving preferred treatment lags behind. Consequently, survival did not improve in the oldest patients.

1. Introduction

Advances in primary treatment of cervical cancer (CC) have found their way into international guidelines and are expected to have influenced survival rates. However, recent studies have shown that CC survival rates have remained stable or increased only slightly worldwide, over the past decades [1,2]. Population-based studies to evaluate whether guideline-recommended treatments have indeed been applied in daily practice are relatively scarce.

For early-stage CC (ECC), guidelines propose primary surgery as the recommended treatment [3,4]. For macroscopically visible tumours, definitive radiotherapy represents an effective alternative—particularly for tumours with unfavourable prognostic and predictive factors for oncological and morbidity outcome. In International Federation of Gynaecology and Obstetrics (FIGO) 2009 stages IB2–IIA2, chemoradiation has been replacing radiotherapy since the late 90s. As an alternative, radical surgery can be performed in lymph node negative patients. In locally advanced CC (LACC) stages IIB or higher, primary chemoradiation currently is the treatment of choice. For metastatic CC (M+), a variety of treatment options may be applied, depending on disease extent and functional status. The inclusion of brachytherapy is recommended in all tumour stages with treatment regimens in which primary radiotherapy is involved.

The probability of being treated as per the guideline declines with increasing age, although studies have shown that older patients may also benefit from standard care [5,6]. Moreover, they are under-represented in clinical trials, making evidenced-based recommendations for older patients difficult [7]. This study aims to report trends in primary treatment and 5-year relative survival (RS) in CC care to identify opportunities to improve clinical practice and, subsequently, disease outcome. A specific focus is placed on differences among tumour stages and age groups.

2. Materials and methods

2.1. Study design and patient selection

We performed a nationwide observational cohort study by analysing data from the Netherlands Cancer Registry, a population-based registry with coverage of all newly diagnosed malignancies in the Netherlands since 1989 [8]. Registration clerks routinely extract information on patient, tumour, and treatment characteristics from medical records within hospitals.

All women newly diagnosed with CC between January 1989 and December 2018, were identified. Patients were followed up until their date of death, date of emigration or end of follow-up (December 31st, 2019)—whichever occurred first. Vital status and date of death or emigration were obtained from the Personal Records Database (BRP). FIGO stages were derived from the Tumour-Nodal-Metastasis (TNM) classification system of malignant tumours, based on pre-treatment clinical examination and imaging. If clinical TNM stage was missing (12%), pathological TNM stage was used (9%).

Several changes to FIGO stages have taken place during the time frame of this study. Stage IA was redefined based on stromal invasion and horizontal spread in 1994. Stage IB and stage IIA were subdivided into lesions $\leq$4 cm and >4 cm in 1994 and 2009, respectively. To avoid irregularities from these changes during analyses, we classified FIGO I–IIA as tumour stage ECC. No major changes have been made to FIGO IIB-IVA and IVB—these were classified as tumour stage LACC and M+, respectively. Patients with FIGO II (without suffix) were classified as LACC, based on interstage comparison of unadjusted RS rates. Patients with any type of distant metastasis, including paraaortic lymph node involvement, were classified as M+.

2.2. Ethics

This study was approved by the Privacy Review Board of the Netherlands Cancer Registry (31/8/2020; K20.283).

2.3. Statistical analysis

Patients were grouped as per year of diagnosis and temporal trends in primary treatment were analysed with the Cochran-Armitage trend test. Five-year RS rates were estimated using the Ederer II method. RS is defined as the ratio of the observed survival among patients with cancer and the expected survival in a group of the general population with similar characteristics [9]. The expected survival rates (stratified by age, sex and calendar year) were obtained from population mortality life tables from Statistics Netherlands (available until January 2020). Traditional cohort analysis was applied

for the period 1989–2014. Period analysis was applied for 2015–2018, as it obtains more accurate survival estimates for recently diagnosed patients [10]. Age-standardised RS rates were estimated using International Cancer Survival Standard 2 [11]. Multivariable Poisson regression was applied—adjusting for age at diagnosis, period of diagnosis, tumour stage, histological subtype and primary treatment—to calculate relative excess risks (RERs) and 95% confidence intervals (CIs). Survival times were censored at five years after diagnosis. Subanalyses on stage IA–IB1 and IB2–IIA2 comprised the period 1999–2018, as subdivision of stage IB was first incorporated in FIGO 1994. Trends in the application of brachytherapy, as part of definitive radiotherapy or chemoradiation, were evaluated. Data on brachytherapy were available from 2004. All analyses were conducted using Stata/SE version 16.1 (Stata Corporation, College Station, TX, USA). Statistical tests were two-tailed and considered significant at $p < 0.05$.

3. Results

3.1. Study population

A total of 21,644 patients were identified (Table 1). Median age at diagnosis was 47 years (interquartile range 37–64). Main tumour stage was ECC ($n = 13,675$; 63%) and most common histological subtype was squamous cell carcinoma ($n = 16,077$; 74%).

Patients were diagnosed more often over time between 45 and 54 years of age (from 16% to 23%; $p < 0.001$) and less often between 65 and 74 years (from 16% to 9%; $p < 0.001$). ECC diagnosis decreased (from 63% to 60%; $p = 0.006$) and M+ diagnosis increased (from 4% to 10%; $p < 0.001$). Adenocarcinoma diagnosis increased from 15% to 20% ($p < 0.001$).

Table 2
Primary treatment for tumour stages of cervical cancer, *n* (%).

Primary treatment	ECC	LACC	M+	Unknown	Total
No therapy	145 (1)	484 (8)	397 (28)	274 (49)	1,300 (6)
Surgery	11,512 (84)	564 (9)	77 (5)	120 (21)	12,273 (57)
Chemotherapy	11 (0)	60 (1)	276 (19)	9 (2)	356 (2)
Radiotherapy	1,077 (8)	2,698 (45)	388 (27)	98 (17)	4,261 (20)
Chemoradiation	900 (7)	2,135 (36)	251 (17)	14 (2)	3,300 (15)
Metastasis only*	0 (0)	0 (0)	38 (3)	0 (0)	38 (0)
Other	4 (0)	6 (0)	8 (1)	4 (1)	22 (0)
Unknown	26 (0)	19 (0)	6 (0)	43 (8)	94 (0)
Total	13,675 (100)	5,966 (100)	1,441 (100)	562 (100)	21,644 (100)

ECC, early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cervical cancer (FIGO IVB).
* No treatment on primary tumour, only on metastasis.

3.2. Trends in primary treatment, by tumour stage

Primary treatment for ECC, LACC and M+ between 1989 and 2018 is reported in Table 2. ECC is predominantly treated by surgery (84%). The most common treatment for LACC is radiotherapy (45%), followed by chemoradiation (36%). In M+, 28% of the patients did not receive any therapy.

Temporal trends in primary treatment are illustrated in Fig. 1. The application of chemoradiation increased over time for all tumour stages ($p < 0.001$)—primarily at the

Table 1
Patient characteristics, *n* (%).

Characteristic	1989–1993 $n = 3,724$	1994–1998 $n = 3,665$	1999–2003 $n = 3,272$	2004–2008 $n = 3,523$	2009–2013 $n = 3,593$	2014–2018 $n = 3,867$	Total $N = 21,644$
Age group							
15–44	1,619 (43)	1,586 (43)	1,428 (44)	1,517 (43)	1,512 (42)	1,666 (43)	9,328 (43)
45–54	583 (16)	655 (18)	611 (19)	716 (20)	760 (21)	892 (23)	4,217 (19)*
55–64	464 (12)	425 (12)	385 (12)	473 (13)	491 (14)	531 (14)	2,769 (13)*
65–74	601 (16)	513 (14)	376 (11)	344 (10)	349 (10)	360 (9)	2,543 (12)*
75+	457 (12)	486 (13)	472 (14)	473 (13)	481 (13)	418 (11)	2,787 (13)
Tumour stage							
ECC	2,359 (63)	2,359 (64)	2,078 (64)	2,274 (65)	2,280 (63)	2,325 (60)	13,675 (63)*
LACC	1,074 (29)	1,015 (28)	923 (28)	909 (26)	935 (26)	1,110 (29)	5,966 (28)
M+	138 (4)	177 (5)	187 (6)	270 (8)	284 (8)	385 (10)	1,441 (7)*
Unknown	153 (4)	114 (3)	84 (3)	70 (2)	94 (3)	47 (1)	562 (3)*
Histological subtype							
SCC	2,759 (74)	2,741 (75)	2,416 (74)	2,649 (75)	2,671 (74)	2,841 (73)	16,077 (74)
ADC	569 (15)	610 (17)	592 (18)	637 (18)	694 (19)	791 (20)	3,893 (18)*
ASC	105 (3)	123 (3)	97 (3)	98 (3)	102 (3)	97 (3)	622 (3)
Other	69 (2)	55 (2)	57 (2)	68 (2)	75 (2)	93 (2)	417 (2)*
Unknown	222 (6)	136 (4)	110 (3)	71 (2)	51 (1)	45 (1)	635 (3)*

ECC, early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cervical cancer (FIGO IVB); **SCC,** squamous cell carcinoma; **ADC,** adenocarcinoma; **ASC,** adenosquamous carcinoma.
*Significant at $p < 0.05$.

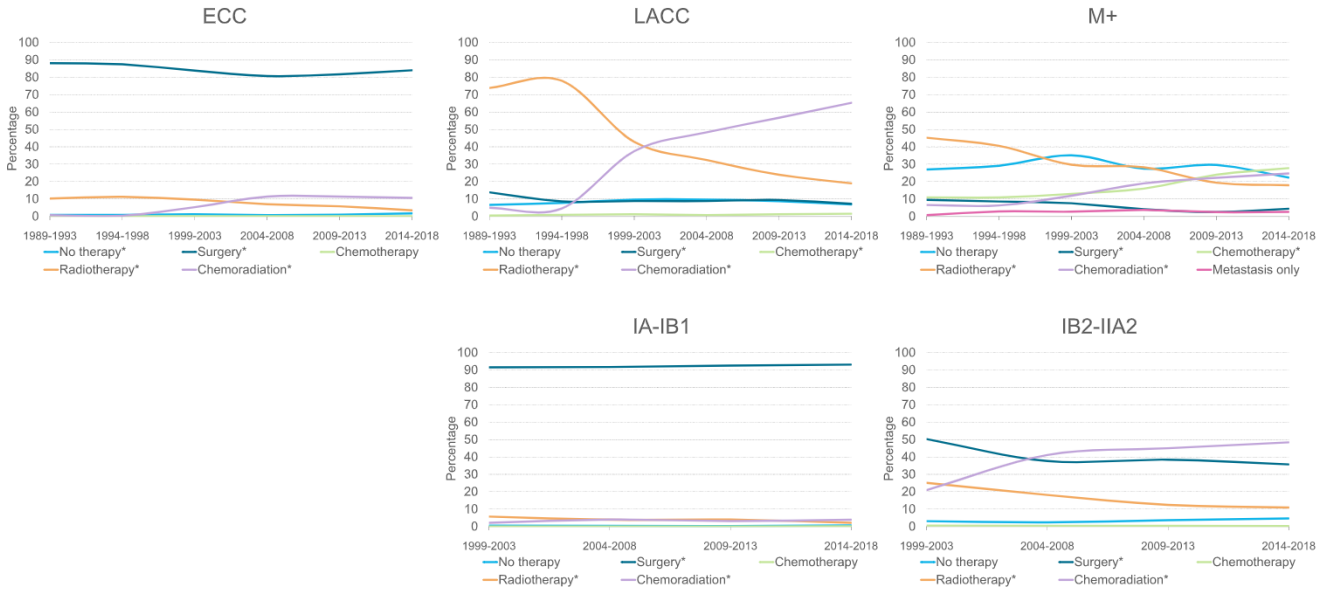

Fig. 1. Temporal trends in primary treatment of cervical cancer, stratified by tumour stages. **ECC,** early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cervical cancer (FIGO IVB). Metastasis only: no treatment on primary tumour, only on metastasis. * Significant at $p < 0.05$.

cost of radiotherapy. Chemoradiation is being applied more frequently than radiotherapy for LACC and M+, since 2004–2008 and 2009–2013, respectively. Analysis on stages IA–IB1 for the period 1999–2018 showed no clinically relevant changes. In stages IB2–IIA2—for the same period—for which surgery and chemoradiation are both guideline-recommended treatments, chemoradiation has become the most widespread treatment in use since 2004–2008.

3.3. Trends in primary treatment, by age groups

Temporal trends in the application of the most common treatment modalities in ECC, LACC and M+ stratified by age groups, are illustrated in Fig. 2. In ECC, surgery was the preferred treatment during all periods, for all age groups between 15 and 74. Overall, it was applied more often in younger compared with older patients (92% in 15–44; 64% in 65–74). For patients aged 75+, radiotherapy has been the most common treatment until 2014–2018, during which it was exceeded by surgery (29% vs. 41%). A decrease over time was observed in the application of surgery for ages 15–54 ($p < 0.001$), against an increase in the administration of chemoradiation ($p < 0.001$). An increase was found in the proportion of 75+ patients refraining from curative therapy (from 4% to 21%, $p < 0.001$).

In LACC, an increase over time was observed in the application of chemoradiation for all age groups ($p < 0.001$). Chemoradiation has surpassed radiotherapy as treatment of choice for all age groups between 15 and 74. The overall percentage of patients that received chemoradiation decreased with increasing age (54% in 15–44; 10% in 75+). For patients aged 75+, radiotherapy use decreased (from 74% to 54%, $p < 0.001$), but remained the most frequently applied treatment. As in ECC, an increase over time was observed in the proportion of 75+ patients refraining from any type of curative therapy (from 15% to 20%, $p = 0.038$).

In M+, the use of chemotherapy increased over time ($p < 0.001$), but varied widely, for all age groups (e.g. 6%–40% in 2014–2018). The use of radiotherapy decreased for all age groups between 15 and 74 ($p \leq 0.007$). For ages 75+, radiotherapy was the most frequently applied treatment until it was exceeded by 'no therapy' from 1999 to 2003 onwards. A decrease was observed in patients refraining from therapy for M+, when aged 15–44 (from 21% to 7%, $p = 0.013$).

Brachytherapy use increased over time in patients treated with chemoradiation, regardless of tumour stage ($p \leq 0.001$) (Fig. 3). It was more often part of treatment in patients treated with chemoradiation than with radiotherapy (81% vs. 57%). In general, brachytherapy was administered least often in 75+ patients. For this group, its use only increased in patients treated with chemoradiation for LACC ($p = 0.018$).

3.4. Trends in relative survival

Temporal trends in 5-year RS rates with 95% CIs and results from multivariable analyses are illustrated in Fig. 4 and reported in Table 3. Average 5-year RS was 71% and age-standardised RS was 66% between 1989 and 2018. For the full cohort, RS increased over time from 68% to 74%. After covariate adjustment, this difference remained significant (RER 0.55; 95% CI

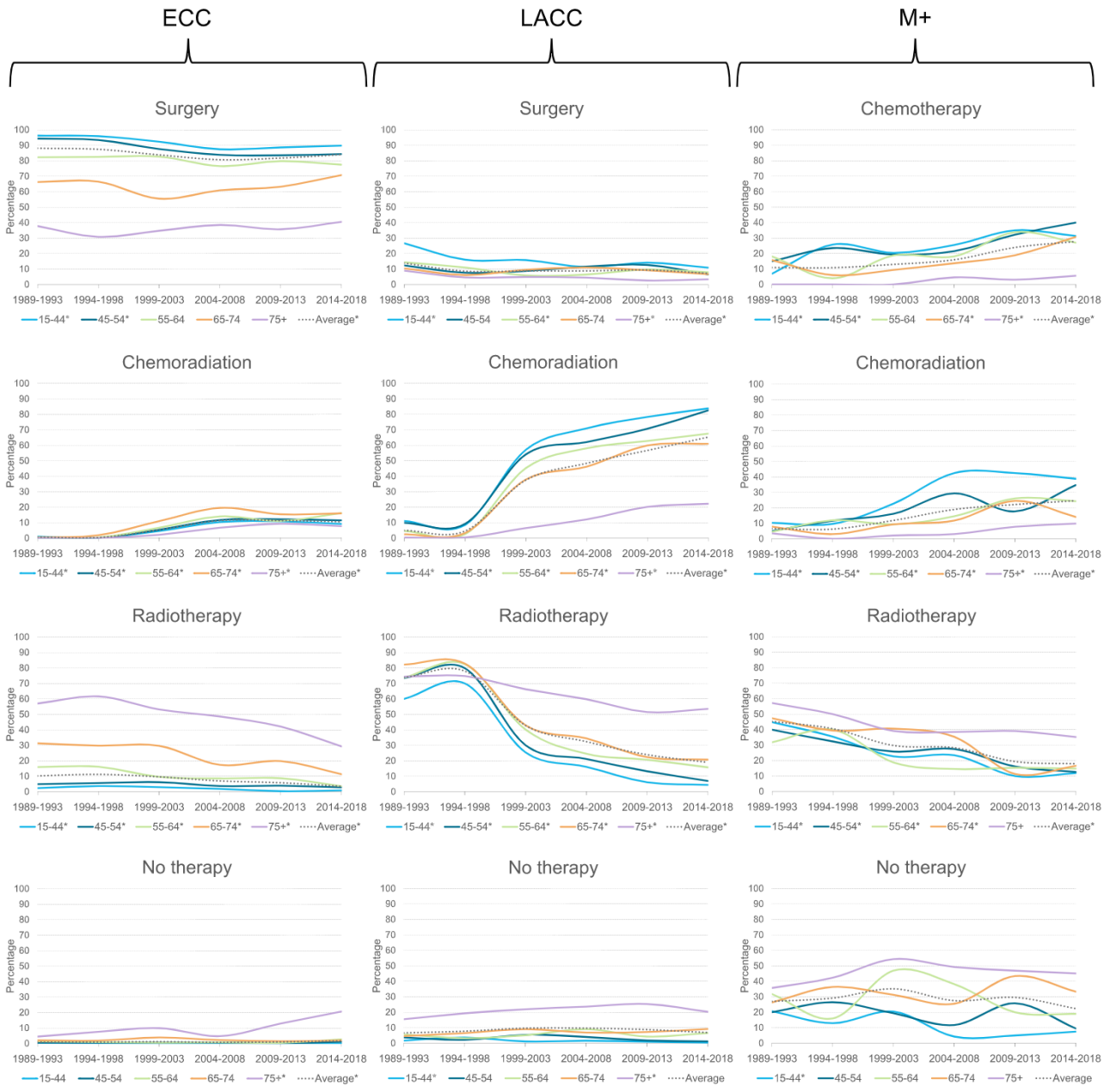

Fig. 2. Temporal trends in the application of the most common treatment modalities, stratified by tumour stages and age groups. **ECC,** early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cervical cancer (FIGO IVB). * Significant at $p < 0.05$.

[0.50–0.62]). Age-standardised RS increased from 62% to 68% (0.53 [0.41–0.67]). Survival rates improved over time for all age groups between 15 and 74. It was stable in patients aged 75+ (0.82 [0.66–1.02]). Increases were also reported for ECC, LACC, M+ and the most common histological subtypes. For stages IA–IB1, the increase from 93% to 95% was significant (0.65 [0.44–0.95]; data not shown). For stages IB2–IIA2, the decrease from 72% to 70% turned out insignificant (0.89 [0.61–1.29]; data not shown).

3.5. Trends in relative survival, by age groups

Temporal trends in 5-year RS rates for ECC, LACC and M+, stratified by age groups, are illustrated in Fig. 5. After covariate adjustment, the increase in RS turned out significant for patients aged 15–64 with ECC. The RS decrease from 60% to 45% in ages 75+, turned out insignificant (1.18 [0.70–1.99]). Survival increased significantly for all age groups in LACC. The most conservative increase (from 30% to 41%) was detected in patients aged

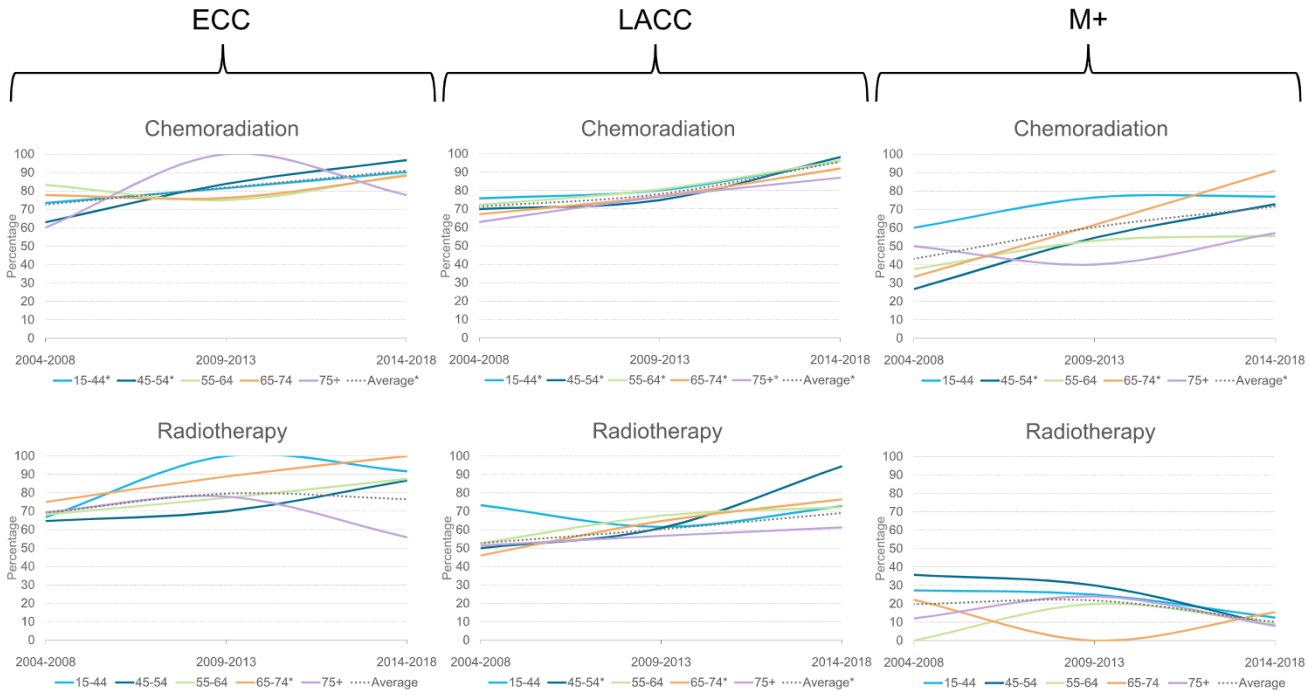

Fig. 3. Temporal trends in the application of brachytherapy as part of treatment with chemoradiation or radiotherapy, stratified by tumour stages and age groups. **ECC,** early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cervical cancer (FIGO IVB). * Significant at $p < 0.05$.

75+ (0.66 [0.49–0.91]). In M+, RS rates only significantly increased for those aged 15–44 and 65–74. For stages IA–IB1, RS did not change for separate age groups. For stages IB2–IIA2, RS only increased in patients between 15 and 44 (0.48 [0.26–0.91]).

4. Discussion

Significant increases in 5-year RS were observed in all tumour stages but not across all ages. Remarkably, it did not improve in ECC patients aged 65–74 and 75+,

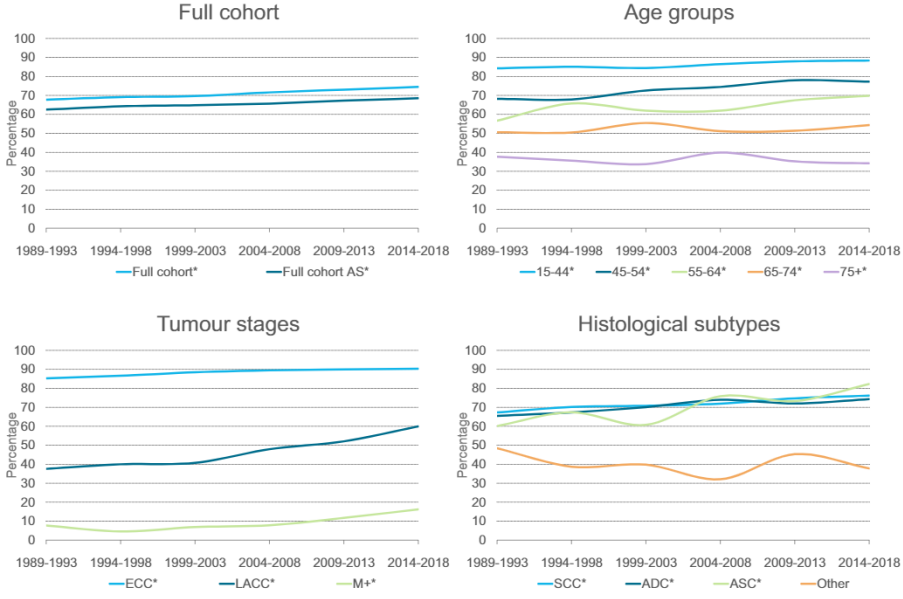

Fig. 4. Temporal trends in 5-year relative survival. **AS,** age-standardised; **ECC,** early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cervical cancer (FIGO IVB); **SCC,** squamous cell carcinoma; **ADC,** adenocarcinoma; **ASC,** adenosquamous carcinoma. * Significant at $p < 0.05$.

Table 3
Temporal trends in five-year survival rates (95% CI) including results from multivariable analyses.

	1989–1993	1994–1998	1999–2003	2004–2008	2009–2013	2014–2018	Total	RER 95% CI	*P*
Full cohort	68 (66–69)	69 (67–71)	70 (68–71)	72 (70–73)	73 (71–75)	74 (73–76)	71 (70–72)	0.55 (0.50–0.62)	0.000
Full cohort AS	62 (61–64)	64 (62–66)	65 (63–67)	66 (64–68)	67 (65–69)	68 (66–71)	66 (65–66)	0.53 (0.41–0.67)	0.000
Age group									
15–44	84 (82–86)	85 (83–87)	84 (82–86)	86 (85–88)	88 (86–90)	88 (87–90)	86 (85–87)	0.39 (0.30–0.50)	0.000
45–54	68 (64–72)	68 (64–71)	73 (69–76)	74 (71–78)	78 (75–81)	77 (74–80)	73 (72–75)	0.42 (0.32–0.54)	0.000
55–64	57 (52–61)	66 (61–70)	62 (57–67)	62 (57–66)	67 (63–72)	70 (65–74)	64 (62–66)	0.61 (0.47–0.79)	0.000
65–74	51 (46–55)	50 (46–55)	55 (50–61)	51 (45–57)	51 (46–57)	54 (48–60)	52 (50–54)	0.50 (0.39–0.65)	0.000
75+	38 (32–44)	36 (30–41)	34 (28–39)	40 (34–46)	35 (30–41)	34 (29–40)	36 (34–39)	0.82 (0.66–1.02)	0.070
Stage									
ECC	85 (84–87)	87 (85–88)	88 (87–90)	89 (88–91)	90 (88–91)	90 (89–92)	88 (88–89)	0.47 (0.37–0.60)	0.000
LACC	38 (34–41)	40 (37–43)	41 (37–44)	48 (44–51)	52 (49–55)	60 (56–63)	47 (45–48)	0.55 (0.47–0.65)	0.000
M+	8 (4–13)	5 (2–9)	7 (4–11)	8 (5–12)	12 (8–16)	16 (12–21)	10 (9–12)	0.70 (0.56–0.88)	0.002
Unknown	56 (46–64)	55 (44–65)	46 (34–58)	26 (15–38)	48 (36–59)	36 (23–51)	48 (43–53)	0.91 (0.54–1.54)	0.729
Histological subtype									
SCC	67 (65–69)	70 (68–72)	71 (69–73)	72 (70–74)	75 (73–76)	76 (74–78)	72 (71–73)	0.55 (0.49–0.63)	0.000
ADC	65 (61–70)	67 (63–71)	70 (66–74)	74 (70–77)	72 (68–75)	74 (71–78)	71 (69–73)	0.46 (0.35–0.59)	0.000
ASC	60 (50–69)	67 (58–75)	61 (50–70)	76 (66–84)	73 (63–81)	82 (73–89)	70 (66–73)	0.25 (0.12–0.52)	0.000
Other	48 (35–61)	39 (25–52)	40 (26–54)	32 (21–44)	45 (33–57)	38 (27–48)	40 (35–45)	0.95 (0.57–1.57)	0.832
Unknown	89 (84–93)	69 (60–76)	64 (54–73)	68 (55–78)	39 (25–53)	23 (12–36)	70 (66–74)	1.33 (0.70–2.51)	0.387

AS, age-standardised; **ECC,** early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cancer (FIGO IVB); **SCC,** squamous cell carcinoma; **ADC,** adenocarcinoma; **ASC,** adenosquamous carcinoma; **RER,** relative excess risk; **CI,** confidence interval.

over a three-decade period. On the other hand, major advances in survival have been observed in patients diagnosed with LACC, with significant survival improvements across all age groups. Even so, it increased the least in LACC patients aged 75+.

Age-standardised 5-year RS increased from 63% to 69%. In a global surveillance of cancer survival trends by Allemani *et al.* [1], 5-year RS was in the range of 60–69% in most of the countries. In a recent Swedish population-based study [12], age-standardised RS was 70% between 2011 and 2015. In this study, more patients were diagnosed with ECC (68% vs. 62%) and more patients with LACC received curative treatment (94% vs. 92%), providing a possible explanation for this difference.

RS of older ECC patients was low, although this stage has a high chance of cure. CC is known to be related with lower socioeconomic status and smoking [13,14]—factors also associated with mortality and comorbid conditions not related to CC [15,16]. Therefore, the other-cause mortality of older CC patients may be significantly higher, compared with the general population of the same age [17], resulting in a low RS. Besides, comorbidity may interfere with surgery or chemotherapy in chemoradiation.

Radical surgery for ECC was centralised to eight medical centres in the Netherlands, in 2005. The introduction of laparoscopic radical surgery started shortly after (2006). Therefore, the independent impact of centralisation and laparoscopy on survival cannot be determined. However, in contrast to Ramirez *et al.* [18], laparoscopy was not associated with adverse oncological outcomes, in the Netherlands [19]. Chemoradiation for LACC was officially incorporated in the national guideline in 2004. However, we observed a dramatic rise in its use immediately after the NCI statement in 1999, albeit being less dramatic in older patients. Albert *et al.* [20] studied patients with IB2–IVA CC. Of those aged 71–80 and > 80, chemoradiation was administered in 63% and 34%, respectively, which is remarkably higher than the 48% and 10% in our study. One probable explanation for the reluctance to administer chemoradiation in older patients is the increased likeliness of intolerable toxicity, compared with radiotherapy [21–23]. In M+, bevacizumab was approved in the Netherlands in 2015, after it was associated with improved survival when combined with traditional chemotherapy, in the GOG 240 trial [24]. In the most recent period of our study, bevacizumab was administered to 13% of the M+ patients receiving chemotherapy. From this limited available data, we cannot confirm, nor deny, an effect on survival.

The necessity of brachytherapy in radiotherapeutic treatment of CC has frequently been emphasised [25–27]. Accordingly, the present study showed a significant increase in its use. However, reports from the United States found a decline in brachytherapy use [25,28]. Two other studies reported that only 33%–54% of the LACC patients aged 70+ received external radiotherapy with brachytherapy, which was lower than in our study (64%) [20,29]. Brachytherapy is often well tolerated in older patients and even those with comorbidities experience survival benefits [20,30].

Among the promising treatment techniques for the future is image-guided adaptive brachytherapy, showing high levels of disease control in ECC and LACC, while reducing morbidity [26,31]. The ongoing EMBRACE II trial (ClinicalTrials.gov identifier: NCT03617133) has

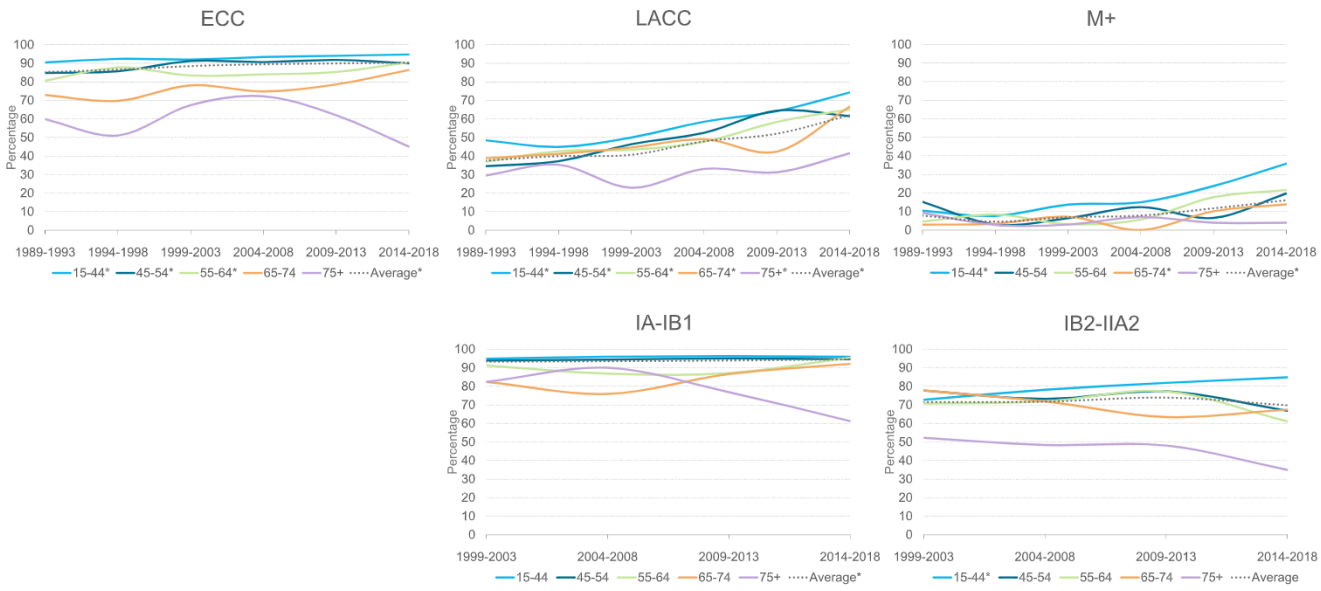

Fig. 5. Temporal trends in 5-year relative survival, stratified by tumour stages and age groups. **ECC,** early-stage cervical cancer (FIGO I-IIA); **LACC,** locally advanced cervical cancer (FIGO IIB-IVA); **M+,** metastatic cervical cancer (FIGO IVB). * Significant at $p < 0.05$.

no age limit in the inclusion criteria, so it may provide good quality data on the feasibility of chemoradiation in older patients [26]. In ECC treatment, the results from the SHAPE trial (NCT01658930) are awaited, in which the non-inferiority of the simple versus the radical hysterectomy in low-risk ECC is being evaluated. Besides, results from the SENTICOL III (NCT03386734) and SENTIX (NCT02494063) studies, investigating whether the sentinel node biopsy is inferior to pelvic lymphadenectomy, will be disclosed in the oncoming years. These treatments might be feasible options, with less morbidity, for older patients. In M+, immunotherapy holds promise, with many ongoing trials in CC [32].

The strength of this study is the use of real-world data from a cancer registry with nationwide coverage since 1989. Furthermore, the high levels of data completeness on tumour stage (97%) and primary treatment (nearly 100%), make results from our analyses reliable. A limitation of this study lies in a disparity between the FIGO and TNM classification on suspected para-aortic lymph nodes. The TNM defines these as non-regional lymph nodes and therefore as distant metastasis. This has resulted in a higher M+ rate than studies using the FIGO classification.

In summary, RS has increased significantly across all tumour stages, over the last three decades. Especially in older patients, the proportion of patients receiving preferred treatment is lagging behind. Consequently, survival improved the least in the oldest patients. Ongoing trials, including older patients, could change the treatment landscape and improve survival.

Author contributions

Hans H.B. Wenzel contributed to conceptualization, methodology, software, formal analysis, investigation, data curation, writing—original draft, and visualization.

Ruud L.M. Bekkers and Valery E.P.P. Lemmens contributed to writing—review and editing.

Maaike A. Van der Aa and Hans W. Nijman contributed to conceptualization and writing—review and editing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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